Uveal Melanoma

Effective Date: June, 2021

Under Review: Until the formal update of this guideline, please consult the most recent Cancer Care Alberta publication in Current Oncology, available at: https://www.mdpi.com/1718-7729/31/1/2/review_report
Background

Melanoma of the uveal tract (i.e., iris, ciliary body, and choroid), sometimes referred to as ‘ocular melanoma’ (Figure 1) accounts for 5% of all melanomas and occurs at an incidence rate of about 6 cases per million person years.\textsuperscript{1, 2} Uveal melanoma is the most common primary intraocular malignancy and the uveal tract is the second most common location for melanoma, after the skin.\textsuperscript{2} Risk factors include Caucasian race, light eye color, fair skin, cutaneous and iris nevi and freckles, and an inability to tan, and exposure to arc welding and suntan beds.\textsuperscript{3-8} Despite these specific similarities to cutaneous melanomas, the association between ultraviolet (UV) light and uveal melanoma has not been clarified.\textsuperscript{4-6, 9}

Uveal melanoma is distinct in molecular pathogenesis, with classically described UVB-induced signature mutations in the cancer genomes restricted to iris uveal melanoma,\textsuperscript{10} and a median count of nine somatic mutations per tumour compared with a median of 171 somatic mutations in cutaneous melanoma.\textsuperscript{11} Driver mutations are also, distinct, commonly affecting GNAQ or GNA11 and BAP1, while mutations in BRAF and NRAD, commonly seen in cutaneous melanoma, are uncommon.\textsuperscript{12}

Uveal melanoma is a distinct clinical entity from other ‘ocular’ melanomas that can arise in the conjunctiva, the eyelid, and the orbit.\textsuperscript{7} Therefore, these guidelines do not apply to melanomas that arise in the conjunctiva, eyelid, and orbit. The choroid is the most common location for uveal melanoma, comprising 80% of cases, the ciliary body 12%, and the iris 8%. Of these topographical locations, the ciliary body carries the worst prognosis, while the iris carries the best.\textsuperscript{13, 14} The Callender histological classification for uveal melanoma identified four distinct cellular types in order of best to worst prognosis: spindle-A cells (slender nuclei and lacking visible nucleoli); spindle-B cells (larger nuclei and distinct nucleoli); intermediate cells (similar to but smaller than epithelioid cells); and epithelioid cells (larger polygonal cells with one or more prominent nucleoli).\textsuperscript{15, 16} Mixed-cell type uveal melanoma (i.e., epithelioid and spindle) is the most common histological subtype of uveal melanoma and carries an intermediate prognosis.\textsuperscript{16}

Roughly 60% of patients with uveal melanoma will succumb to metastasis within 10 years, but varies based on tumour size and other prognostic factors, including cell type, location of the anterior margin of the tumour, degree of ciliary body involvement, extraocular extension, mitotic rate, and lymphocytic infiltration.\textsuperscript{13, 14, 17, 18} Survival is 47% at 10 years and 25% at 20 years (Table 1). Using modern genetic prognostic testing (gene expression profiling) further prognostic information can be obtained (Table 2). The overall local recurrence rate following plaque brachytherapy is approximately 10% at five years (median 25.5 [12-71] months).\textsuperscript{19} The most common site of metastasis is the liver and the second most common is the lungs. Few clinical trials focused solely on metastatic uveal melanoma, therefore treatment decisions in the palliative setting are often based upon data from studies conducted in the non-uveal melanoma patient population. Low quality evidence exists to support the use of immune checkpoint inhibitors for the treatment of patients with metastatic uveal melanoma, and recently an improvement in overall survival (OS) for patients with metastatic uveal melanoma treated with the novel immunotherapy tebentafusp was reported.\textsuperscript{20}
Figure 1. The choroid, ciliary body, and iris make up the uvea which contains the neural crest derived melanocyte and its associated malignant potential. Medical illustration: Robert Masini

Table 1. Long-term survival estimates associated with uveal melanoma.18, 21

<table>
<thead>
<tr>
<th>Survival Measure</th>
<th>5-year</th>
<th>10-year</th>
<th>15-year</th>
<th>20-year</th>
<th>25-year</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-Cause Survival</td>
<td>62%</td>
<td>47%</td>
<td>35%</td>
<td>25%</td>
<td>21%</td>
</tr>
<tr>
<td>Melanoma Metastasis-Free Survival</td>
<td>69%</td>
<td>60%</td>
<td>55%</td>
<td>52%</td>
<td>51%</td>
</tr>
<tr>
<td>Second Cancer-Free Survival</td>
<td>95%</td>
<td>89%</td>
<td>85%</td>
<td>79%</td>
<td>76%</td>
</tr>
</tbody>
</table>

Table 2. Metastasis-free survival by signature class (i.e., gene expression profile).18, 21, 22

<table>
<thead>
<tr>
<th>Signature Class</th>
<th>3-year</th>
<th>5-year</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A</td>
<td>98%</td>
<td>98%</td>
</tr>
<tr>
<td>1B</td>
<td>93%</td>
<td>79%</td>
</tr>
<tr>
<td>2</td>
<td>50%</td>
<td>28%</td>
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The common differential diagnosis for uveal melanoma includes lesions such as nevus, neovascular (‘wet’) age-related macular degeneration, congenital hypertrophy of the retinal pigment epithelium, circumscribed choroidal hemangioma, hemorrhagic detachment of the choroid or retina, melanocytoma, metastasis to the eye from another site and choroidal osteoma.23

Guideline Questions

1. How should patients with uveal melanoma be staged at baseline?
2. How should uveal melanoma, including patients who experience metastatic or recurrent disease, be managed?
3. What is the recommended surveillance strategy for patients diagnosed with uveal melanoma?
Search Strategy

For the 2021 guideline update, PubMed was searched (2014 through 2021 Mar) for phase II and III clinical trials, prospective studies, systematic reviews, meta-analyses, and clinical practice guidelines. The Medical Subject Heading (MeSH) term “uveal melanoma” was used, and results were limited to studies in humans 19+ years of age published in English. Studies that did not report outcomes related to the efficacy of treatments or imaging modalities for uveal melanoma and studies involving less than ten patients were excluded. Reference lists of key publications were also searched for relevant citations. For the detailed literature search strategy, results and a summary of key evidence please refer to the accompanying evidence table.

The ECRI Guidelines Trust, well-known cancer guideline developers and Google (search term: “uveal melanoma guideline”) were searched for practice guidelines relevant to this topic. A total of eight clinical practice guidelines published after 2014 were identified from the following organizations: UpToDate, National Comprehensive Cancer Network (NCCN), National Cancer Institute (NCI), Cancer Council Australia, European Dermatology Forum (EDF) / European Association of Dermato-Oncology (EADO) / European Organization for Research and Treatment of Cancer (EORTC), National Services Division (NSD) Scotland, United Kingdom Uveal melanoma Guideline Working Group, Princess Margaret Cancer Centre.

Target Population

The recommendations outlined in this guideline apply to adults over the age of 18 with malignant uveal melanoma (intra-ocular melanoma). Other 'ocular' melanomas arising in the conjunctiva, the eyelid, and the orbit are not included in this guideline. Different principles may apply to pediatric principles.

Recommendations

Diagnosis and Work-Up

1. All intraocular malignancies and indeterminate lesions should be evaluated by a provider trained in all aspects of care (i.e., medical, oncologic, surgical, radiotherapy [RT], laser therapy [e.g., transpupillary thermotherapy]) to determine appropriate follow-up and/or treatment. (*Level of Evidence: V*24-26, *Strength of Recommendation: B*)

2. Complete history including ophthalmic and medical history.

3. Complete ophthalmic examination and fundoscopy.

   - A baseline fundus photograph of adequate quality and an objective assessment of lesion height is required for all melanocytic lesions.
4. Ocular ultrasonography by a certified ophthalmic ultrasonographer or ophthalmologist with training in ultrasound (U/S).
   - A-scan U/S can demonstrate initial prominent spike followed by low-to-medium internal reflectivity or a decrescendo pattern and can be used to measure tumour height. (Level of Evidence: IV$^{27}$, Strength of Recommendation: B)
   - B-scan U/S can allow for tumour measurement (height), and tumour characteristics including solidity/hollowness, vascularity, shape, and extra-scleral (extraocular) extension. (Level of Evidence: IV$^{27}$, Strength of Recommendation: B)
   - U/S biomicroscopy (UBM) is a high frequency U/S providing high resolution imaging of the anterior segment of the eye. It is used to visualize ciliary body and iris tumours. (Level of Evidence: IV$^{28}, 29$, Strength of Recommendation: B)

5. Ancillary ocular studies, if ophthalmic examination is inconclusive, sometimes due to media opacity. (Level of Evidence V$^{30-32}$, Strength of Recommendation: B)
   - Fluorescein and/or Indocyanin green angiography of the retina and choroidal vasculature is helpful in select cases (requires clear media for visualization).
   - Computed tomography (CT) of the eye is rarely needed.
   - Magnetic resonance imaging (MRI) of the eye is rarely needed.

6. Staging work-up to rule out metastases for patients diagnosed with uveal melanoma.
   - Serum testing
     - Complete blood count (CBC)
     - Liver function tests (LFTs)
   - Diagnostic imaging should aim to reduce unnecessary radiation.
     - All patients should receive a baseline Primovist-enhanced abdominal MRI and ultrasound (U/S) of the liver and non-contrast enhanced CT scan of the chest.
     - Or whole-body positron emission tomography (PET)/CT scan and ultrasound of the liver. (Level of Evidence: II$^{33}$ IV$^{34}$, Strength of Recommendation: B)
     - If there is a suspicion of metastases, refer to a tertiary cancer centre.

**Primary Management**

**Melanocytic Choroid Tumours**

1. Small (<3 mm in thickness) tumours (i.e., ‘nevii’, ‘indeterminate melanocytic lesions’, and small melanomas)
• Small lesions are observed for growth or treated based on risk factors for growth and the associated risk of visual loss with treatment.
  o Most lesions with no risk factors are observed until growth is documented. Once growth is documented the lesion is labeled a melanoma and is treated. *(Level of Evidence: IV\textsuperscript{35-39}, Strength of Recommendation: B)*
  o All lesions are evaluated based on their risk factors for future growth.
    □ Risk factors for future growth include tumour thickness >2 mm, subretinal fluid, symptoms of visual acuity loss to 20/50 or worse, orange pigment, hollow acoustic density and tumour largest basal diameter >5 mm. *(Level of Evidence: IV\textsuperscript{40}, Strength of Recommendation: B)*
    □ High-risk lesions (≥ 3 risk factors) are often offered treatment, biopsy, or close observation based on discussions with the patient regarding visual loss, since the risk of future growth is greater than 50%. *(Level of Evidence: IV\textsuperscript{41} V\textsuperscript{31}, Strength of Recommendation: B)*
    □ When indicated, treatment is most commonly ocular brachytherapy. *(Level of Evidence: III\textsuperscript{42} IV\textsuperscript{43}, Strength of Recommendation: B)*

2. Medium/intermediate (3-12 mm in thickness) tumours are typically treated with ocular brachytherapy. *(Level of Evidence: I\textsuperscript{44-48}, Strength of Recommendation: A)*
  • Enucleation is sometimes chosen by patients who cannot make the follow-up visits required post brachytherapy.

3. Large (>12 mm in thickness) tumours
  • Due to the risk of severe vision loss and neovascular glaucoma secondary to radiation complications with large lesions, large lesions are offered enucleation or brachytherapy (if standard dosing can be achieved with brachytherapy).
    o Many centres offer enucleation for very large tumors greater than 12 mm in thickness and 18 mm in maximal width. *(Level of Evidence: IV\textsuperscript{49-52}, Strength of Recommendation: B)*
    o Brachytherapy for very large lesions (>12 mm thick or >18 mm in maximal basal dimension) is sometimes performed in select cases such as contralateral vision loss or in patients who insist on avoiding enucleation. *(Level of Evidence: V\textsuperscript{24}, Strength of Recommendation: C)*
  • Neo-adjuvant pre-enucleation radiation does not provide a clinically or statistically meaningful difference in mortality rates. *(Level of evidence: I\textsuperscript{53}, Strength of recommendation: E)*
**Ciliary Body Lesions**

1. Ciliary body lesions <12 mm thick and that do not have an extensive circumferential growth pattern are most commonly treated with brachytherapy. *(Level of Evidence: IV\(^54\) V\(^55\), Strength of Recommendation: C)*

2. Ciliary body lesions are amenable to surgical excision (i.e., iridocyclecomy) in select cases. *(Level of Evidence: IV\(^56\) V\(^23\), Strength of Recommendation: C)*

**Iris Lesions**

1. Iris lesions are typically observed for growth before brachytherapy treatment is offered. *(Level of Evidence: IV\(^57\), Strength of Recommendation: C)*

2. Iris lesions are amenable to surgical excision (i.e., iridectomy) in select cases. *(Level of Evidence: V\(^23\), \(^58\), Strength of Recommendation: C)*

3. Iris lesions are often also amenable to brachytherapy. *(Level of Evidence: V\(^23\), \(^59\), Strength of Recommendation: C)*

**Principles of Complete Assessment**

1. Lesions being observed require a complete assessment of:
   - The current risk factors for growth
   - Adequate baseline photographic imaging of the lesion
   - An objective assessment of the lesion’s thickness to allow assessment for growth
   - Intermittent follow-up imaging is also required to document change or stability of the lesion.

2. Adequate photographic imaging requires:
   - The entire lesion and the adjacent normal structures need to be photographed. Otherwise, growth cannot be truly assessed.
     - In addition, a photograph of the entire lesion including the fovea and the optic nerve is recommended (but not required) to ensure reproducibility of the landmarks adjacent to the lesion.
   - Some very anterior choroidal lesions and ciliary body lesions cannot be photographed in the entirety due to technical limitations in current imaging technology.
   - The lesion needs to be in focus, and appropriate exposure levels in the baseline and follow-up imaging allowing for assessment of change over time need to be obtained.
   - If adequate imaging cannot be obtained, referral to a specialist capable of performing a complete assessment is required.
If two or more risk factors are present or any change or growth is noted, referral to a subspecialist ocular oncologist is recommended.

**Principles of Enucleation**

1. Enucleation involves surgical removal of the eye.

2. Typically, lesions >12 mm in thickness and/or >18 mm in diameter are offered enucleation.

3. For patients undergoing enucleation, in accordance with the College of American Pathologists’ *Protocol for the Examination of Specimens from Patients with Uveal Melanoma,* review of specimens should include reporting of the following elements:
   - Specimen laterality
   - Tumour site: iris, ciliary body, choroid
   - Largest basal diameter and thickness
   - Scleral and optic nerve invasion
   - Extraocular extension
   - Histologic type: spindle, mixed, epithelioid
   - Mitotic count
   - Vascular invasion
   - Extravascular matrix pattern
   - Inflammatory cells/tumour infiltrating lymphocytes and macrophages
   - Invasion of Bruch’s membrane
   - Margins
   - Regional lymph nodes
   - Pathologic stage classification (pTNM, AJCC 8th Edition)
   - Molecular results (if known):
     - Chromosome 3 and 8 loss/gain
     - BAP1 status
     - Gene expression profile (GEP)
     - Multiplex ligation dependent probe amplification (MLPA) analysis
   - Additional pathologic findings
Principles of Primary Radiotherapy (RT)

1. Episcleral brachytherapy is the most commonly utilized treatment for uveal melanoma worldwide and is the treatment of choice in Alberta.

2. Other RT modalities include charged-particle external beam RT (EBRT) (i.e., protons, carbon ions, or helium ions), and photon-based radiosurgery (i.e., linear accelerator, gammaknife, or cyberknife).

Adjuvant Local Therapy

1. Positive margins post excision:
   - If margins are positive or indeterminate after resection, adjunctive plaque brachytherapy RT of the surgical margins is often utilized.

2. Transpupillary thermotherapy (TTT):
   - TTT uses an infrared laser administered through a dilated pupil for choroidal lesions.
   - TTT as a primary treatment has been associated with a relatively high rate of local recurrence, especially when the tumour abuts the optic nerve and overhangs the optic disc. Therefore, TTT is not recommended as monotherapy for uveal melanoma in the standard case. (Level of Evidence: II61 IV62, Strength of Recommendation: D)
   - TTT can be offered as an adjunctive treatment to reduce the risk of local recurrence following RT or as a primary treatment for medium risk nevi in select cases. (Level of Evidence: IV63, 64, Strength of Recommendation: C)
   - TTT is used in some centers to treat marginal recurrence post brachytherapy. (Level of evidence: IV64, Strength of Recommendation: C)
   - TTT can cause retinal vascular damage and retinal traction and subsequent secondary visual loss.

3. Radiation retinopathy:
   - Intravitreal anti-vascular endothelial growth factor (VEGF) agents are often utilized to prevent and/or reduce the severity of radiation retinopathy and its associated visual loss. (Level of Evidence: ranibizumab II65, 66 bevacizumab IV67-70, Strength of Recommendation: B)

Genetic Prognostic Testing

1. All patients should be offered GEP or monosomy 3 and 8 testing to provide information on survival prognosis. This will also guide systemic follow-up and consideration for inclusion in clinical trials.
for patients at high risk of metastases (Figure 2, Table 2). *(Level of Evidence: III\textsuperscript{71, 72} IV\textsuperscript{22, 73-75}, Strength of Recommendation: B)*

**Management of Patients with Metastatic Disease and High-Risk Patients**

1. Currently there is no strong evidence to treat high-risk patients (monosomy 3 and 8q gain, GEP 2, or tumours >9 mm thick) without identified metastasis with adjuvant treatments to reduce the risk of disease recurrence. However, the use of systemic therapy as adjuvant treatment to enucleation or definitive radiation is an active focus of research, and consideration for enrollment in clinical trials is warranted where possible. *(Level of Evidence: IV\textsuperscript{76}, Strength of Recommendation: B)*

2. Systemic therapy for the management of metastases:

   - When possible, enrollment in a clinical trial is recommended.

   - A phase III clinical trial comparing treatment with tebentafusp against investigator’s choice chemo-/immunotherapy in advanced uveal melanoma patients with positive HLA-A 02:01 haplotype achieved its primary end point of OS in the intent-to-treat population with a hazard ratio (HR) of 0.51 (95% CI, 0.36-0.71; p<0.0001), favouring tebentafusp over investigator’s choice of therapy (1-year OS 73 vs 59% median OS 22 vs 16 months) *(Level of Evidence: I\textsuperscript{20}, Strength of Recommendation: A)*

   - A prospective, non-comparative phase II clinical trial demonstrated an overall response rate (ORR) of 18% and a median OS of 19.1 months in a cohort of patients treated with the combination of ipilimumab and nivolumab. *(Level of Evidence: ipilimumab and nivolumab II\textsuperscript{77}, Strength of Recommendation: B)*

   - Objective tumour responses have been documented with the use of pembrolizumab and nivolumab as monotherapy. *(Level of Evidence: pembrolizumab III\textsuperscript{78} nivolumab II\textsuperscript{79}, Strength of Recommendation: B)*

   - Outside of a clinical trial, the routine use of palliative cytotoxic chemotherapy is not recommended; the use of chemotherapy for the treatment of patients with metastatic ocular melanoma is associated with very low objective response rates and has never been shown to extend OS. *(Level of Evidence: I\textsuperscript{80, 81} II\textsuperscript{82-98}, Strength of Recommendation: D)*

3. Surgical resection of solitary/oligo liver metastasis may offer benefit in highly selected patients; most patients who present with metastatic disease present with diffuse involvement of the liver and therefore, do not qualify for surgical resection. *(Level of Evidence: III\textsuperscript{99} IV\textsuperscript{100, 101}, Strength of Recommendation: C)*

4. Ablative techniques (i.e., thermoablation, radioembolization) are used in the setting of metastatic uveal melanoma, with higher-quality evidence in support of radioembolization. *(Level of Evidence: II\textsuperscript{102} IV\textsuperscript{103} V\textsuperscript{104, 105}, Strength of Recommendation: C)*
Surveillance Following Definitive Local Therapy

In patients who would qualify for treatment of metastatic treatment, surveillance should be offered. This may consist of history and physical exam, chemistry, and imaging based on patient risk categories:

1. Patients with GEP class 1a or 1b, or disomy 3 (monosomy 3 negative or undetected) OR patients with no genetic assessment and tumour ≤9 mm thick: *(Level of Evidence: V, Strength of Recommendation B)*
   - Liver U/S: annually for up to 10 years.
   - Physical exam: annually, for up to 10 years.
   - Follow-up may be transitioned to the family physician at 5 years.

2. Patients with GEP class 2, monosomy 3 (monosomy 3 positive or detected), OR tumours >9 mm thick with no genetic assessment: *(Level of Evidence: V, Strength of Recommendation B)*
   - Physical exam: annually, indefinitely
   - Imaging every six months consisting of an annual liver U/S alternating with annual MRI liver for ten years. If body habitus limits U/S, consideration for other modalities should be given.
   - Follow-up may be transitioned to the family physician at 5-10 years.

Discussion

Diagnosis

The timely management (including observation) of uveal melanocytic lesions, including small flat lesions, is vitally important, as this is a major/complex eye condition that threatens both complete visual loss and life. Any delays in referral and treatment may result in both complete loss of the eye (enucleation) and/or life (metastasis).

Research has demonstrated that earlier treatment, allowing for treatment of a smaller lesion, portends improved survival. Furthermore, waiting for observation of growth, in small lesions identified as high-risk by an ophthalmologist, can increases the risk of metastasis by eight times. Therefore, even melanocytic lesions ≤2 mm in thickness without any documentation of growth can be offered treatment. The diagnosis of uveal melanoma can be very difficult for the non-specialist. Treatment options for uveal melanocytic lesions involve both medical, laser, complicated extraocular and intraocular surgery, RT, radiosurgery, and other eye sparing treatment modalities. Often observation versus treatment discussions, especially for small melanocytic lesions, require balancing treatments and their complications with the risk of observation and its threat to life; therefore, published international guidelines, with Canadian representation, recommend that patients be provided an evaluation/discussion with an eye cancer specialist (eye cancer specialist is defined as an ophthalmic oncologist, medical physicist, or radiation oncologist) or ophthalmologist.
to reduce the risks of local recurrence and to reduce the extent of visual loss following eye sparing treatments, adjuvant medical, laser, and complicated surgical treatments often need to be administered.\textsuperscript{53, 67, 110, 111} For these reasons it is recommended that the provider be fully trained in all treatment areas (i.e., medical, complicated surgical, RT, laser treatments of the eye, and cancer care) to safely follow, discuss, and treat all indeterminate (uveal melanocytic lesions that have not demonstrated growth) and malignant intraocular lesions.

Ocular U/S is used to determine tumour size, shape, and the lesion’s U/S characteristics. Orbital/ocular CT and MRI are not commonly required in the diagnostic work-up, unless other examinations are inconclusive.\textsuperscript{32, 108} The common lesions on the differential diagnosis for uveal melanoma includes freckles, nevus, Lisch nodules, neovascular age-related macular degeneration, congenital hypertrophy of the retinal pigment epithelium, choroidal hemangioma, hemorrhagic detachment of the choroid or retina, melanocytoma, metastasis to the eye from another location, and choroidal osteoma. Experienced ocular oncologists (ophthalmologists with a practice focus in oncology) are able to diagnose uveal melanoma accurately (based predominantly on fundoscopy and ultrasound) with >98% accuracy without biopsy.\textsuperscript{45}

**Staging**

Staging is guided by the American Joint Committee on Cancer (AJCC) system for uveal melanoma.\textsuperscript{112} Staging requires intraocular examination, serum tests, and imaging. Blood work typically consists of complete blood count (CBC) and liver function tests (LFT).\textsuperscript{32} Historically, the most basic baseline imaging for ruling out systemic metastases consisted of chest x-ray (CXR) with abdominal U/S. However, these tests have since been shown to have low sensitivities\textsuperscript{113} and have largely been replaced by positron emission tomography (PET)-CT scanning, MRI of the abdomen and CT of the chest, or CT of the chest and abdomen. Whole body PET-CT scan has demonstrated good sensitivity (35-100%) and positive predictive value (88-100%),\textsuperscript{114-116} while MRI has shown the highest sensitivity (67-92%).\textsuperscript{115-117} Table 3 summarizes the accuracy of these various imaging modalities in the detection of uveal melanoma.

Controversy exists around whether baseline imaging should be performed in this population, based on the premise that metastases cannot be treated and the yield of positive findings at presentation is low (2%). It should be noted, however, that more than half of patients (55%) have CT abdomen findings that require further investigation,\textsuperscript{118} the majority of which are false positives; only 2% have definitive metastasis at staging.\textsuperscript{118} An international, registry-based retrospective data analysis of patients presenting with stage IV uveal melanoma found that 6% of the uveal melanoma with metastasis at initial presentation belonged to subcategory T1a, most often detected by whole-body PET/CT.\textsuperscript{34} Therefore, it may be best to clarify these baseline imaging findings early on to reduce the challenges of ruling out metastasis at a later date. The treating surgeon should decide on the appropriateness of staging investigations that balance excessive testing with patient stress, additional testing that can arise from false positives, and potentially unnecessary surgery. Patients who demonstrate metastasis at presentation may be spared aggressive treatment of their primary lesion.
Genetic Prognostic Testing

Two modern prognostic tests that require tumour sampling are currently available, including assessment of monosomy 3 and 8 gain status and GEP. Both tests are typically performed with a fine needle aspiration biopsy at the time of definitive treatment. Monosomy 3 associated with a gain in 8q, and GEP class 2 carry a poor prognosis with a 3-year metastasis free survival of 53% and 50% respectively. Due to the better biopsy yields and stronger evidence on prognostication, in Alberta, the commercially available GEP is now utilized instead of monosomy 3 testing (Figure 2, page 16, Table 2). A controlled prospective clinical observational trial that examined the psychosocial impact of prognostic genetic testing in uveal melanoma patients found that rather than being a burden, it may help to ease stress and support a more realistic risk perception.

Primary Management

**Observation.** Observation is typically reserved for indeterminate lesions, but may be acceptable for select patients with small melanoma (<3.0 mm apical height and <10.0 mm basal diameter) under the direction of an ocular oncologist. Most observed melanoma patients present with a low-grade tumour and have multiple comorbidities or advanced age and already carry a limited expected survival.

Risk factors for future growth of indeterminate lesions include tumour thickness >2 mm, subretinal fluid, symptoms of visual acuity loss to 20/50 or worse, orange pigment, hollow acoustic density and tumour largest basal diameter >5 mm. If these risk factors are present, treatment should be considered. Waiting for documented growth of lesions can increase the risk of metastasis up to eight-fold and improved survival has been demonstrated with earlier management. Similarly, the eight edition of the AJCC classification system has demonstrated that tumour size predicts survival. Furthermore, even after controlling for GEP, tumour size has been found to be an independent predictor of metastasis at 5 years. In contrast, several small non-comparative case-series have suggested that patients with small indeterminate lesions who are carefully selected by an ophthalmologist, may be observed for tumour growth before initiating treatment without adversely affecting survival. The American Brachytherapy Society guidelines suggest that patients being observed should be counseled about the small (yet still unquantified) increased risk of metastasis with observation.

Lesions are often labeled as high-risk nevi or indeterminate melanocytic lesions if they have 3 or more risk factors for growth. Several small, underpowered, retrospective studies suggest there may be a roll in certain situations to observe small lesions. A retrospective analysis of data from patients with primary posterior uveal melanoma with documented tumour growth of ≥3 mm in basal diameter, 1.5 mm in thickness, or both (n=30), during a pretreatment interval of ≥6 months was compared with data from a control group of promptly treated patients (n=30). The resulting mean ± standard error cumulative 5-year probability of melanoma-specific mortality relative to the date of initial examination was 17.1% ± 7% in the delayed group vs. 18.4% ± 8% in the promptly treated group (p>0.5, log rank test). Although this study is underpowered, it and several other similar studies suggest that delaying
treatment in carefully selected patients may not worsen survival. In contrast, retrospective data on a large dataset of 1287 patients suggested that waiting for documentation of growth for lesions <3 mm increased the risk of metastasis eight-fold.107

**Surgical resection.** Local resection of the tumour can preserve the eye but is best suited for iris melanomas and selected ciliary body melanomas or anterior small choroidal melanomas.23 Enucleation involves surgical removal of the eye and has been the most widely used treatment, historically, until advances in RT.23, 122, 123 Typically, lesions >12 mm in thickness and/or >18 mm in diameter are offered enucleation. Concern over whether enucleation was promoting the release of tumour cells throughout the body, leading to observed increases in mortality post-enucleation,123 contributed to the development of new management strategies, such as RT and TTT. Since then this Zimmerman hypothesis on seeding of tumour during enucleation has been disproved.124

**Radiotherapy (RT).** RT has largely replaced enucleation for tumours with suitable location and dimension (i.e., <12 mm in thickness and <18 mm in largest basal diameter). Larger tumours carry a significant risk of severe vision loss and radiation complications; however, RT is sometimes utilized in large tumour patients with a strong preference for attempting eye-sparing treatments. RT options include episcleral brachytherapy, charged-particle external beam RT (i.e., protons, carbon ions, or helium ions), and photon-based radiosurgery (i.e., linear accelerator, Gamma Knife, or CyberKnife).

Brachytherapy provides an accurate and continuous administration of radiation and has the added benefit over enucleation of vision preservation and improved cosmesis.44 Isotopes most commonly used for episcleral plaque brachytherapy include Iodine-125 (125I), Palladium-103 (103Pd), and Ruthenium-106 (106Ru).125 Treatment with 106Ru is often limited to tumours with an apex height of less than 5 mm, but has been shown to be sufficient for treating up to 7mm in small case series.126 Use of 125I is consistent with the methods used in the Collaborative Ocular Melanoma Study (COMS), but 103Pd may be considered for use as the two respective isotopes offer differences in intraocular dose distribution. In Alberta, episcleral plaque brachytherapy is the treatment of choice for small to medium sized melanomas (<10 mm thick and <18 mm in largest basal dimension). High-risk indeterminate melanocytic lesions (i.e., those with ≥3 risk factors) are also typically offered treatment in select cases because the risk of future growth is greater than 50%.107, 127 Brachytherapy is preferred over enucleation as a large randomized controlled trial of 1337 patients has demonstrated no difference in survival between brachytherapy and enucleation,48 and the potential for vision preservation, the emotional challenges of losing an eye, and the improved cosmesis.

The goal of treatment is to deliver a dose of 70 Gy to the apex of the tumour (accounting for attenuation from the silastic and backscatter from the gold plaque), while ensuring the entire base of the tumour is also treated to at least 70 Gy. A 2 mm margin around the base is typically used. Prescription specification, radiation treatment planning, and dose calculations are performed in accordance with published guidelines.128, 129 The dose is calculated with a model-based algorithm which corrects for heterogeneities in the eye plaque, as described by the American Association of Physicists in Medicine.130
The use of a calculation method that corrects for plaque heterogeneities differs from the homogeneous medium calculation method used in the original COMS study, resulting in a difference between the treatment goal of 70 Gy recommended in these guidelines and the 85 Gy used in the COMS study and commonly cited in the literature. This can be explained, however, as a dose of 70 Gy calculated using the more accurate method which includes heterogeneities is roughly equivalent to 85 Gy using the homogeneous method. A review of 53 cases treated in Alberta found the 70 Gy accounting for plaque heterogeneities was equivalent to $81.8 \pm 2.2$ Gy utilizing the COMS methodology.\textsuperscript{131}

The dose is delivered over 3-7 days, as per the recommendations of the American Brachytherapy Society.\textsuperscript{132} Whenever possible, plaque size and shape, plaque loading, and plaque position are chosen such that doses to critical structures such as the fovea, papillomacular bundle, and optic nerve head are minimized. The fovea and papillomacular bundle are retinal tissue with an assumed tolerance of 50 Gy and the optic nerve head has an assumed tolerance dose of 60 Gy.\textsuperscript{128, 129, 133, 134} While reports on the exact radiation tolerance of these tissues vary, it is clear that tumour proximity and radiation dose to these structures are associated with poorer visual outcomes.\textsuperscript{134}

The COMS randomized trial of $^{125}$I brachytherapy vs. enucleation as primary therapy for medium sized melanomas found no difference in survival outcomes and little difference in quality-of-life outcomes between groups. Five-year survival was substantially better than expected based on published rates.\textsuperscript{45, 46, 48, 125} A retrospective case-series among patients diagnosed with uveal melanoma without metastases (N=400) and treated with $^{103}$Pd brachytherapy (mean apical dose of 73.3 Gy over 5 to 7 continuous days) revealed a local control rate of 96.5%. Fourteen patients required secondary enucleation (5 for tumour growth and 9 for glaucoma pain control). The expected 5- and 10-year metastases-free survival rates were 92.7% and 86.6%, respectively.\textsuperscript{135} Low recurrence rates were reported for $^{125}$I brachytherapy as well, in a retrospective analysis of data from 87 patients with uveal melanoma ≤16 mm by largest basal diameter and large by height by the COMS criteria.\textsuperscript{47} The COMS trial found that the risk of treatment failure (i.e., tumour growth, recurrence, or extrascleral extension) with $^{125}$I brachytherapy was 10.3% (95% CI, 8.0%-13.2%). The Kaplan-Meier estimate of proportion of patients undergoing enucleation by 5 years was 12.5% (95% confidence interval [CI], 10.0%-15.6%). Risk factors for treatment failure were older age, greater tumour thickness, and proximity of the tumour to the foveal avascular zone. Tumour control by RT is typically 95% (95% CI 93-96%) at 15 years.\textsuperscript{136} Except for select centers, the majority of radiation treatment for uveal melanoma is administered through brachytherapy. This technique provides extremely accurate administration of radiation to a mobile organ and provides theoretical advantages due to its continuous dose administration. Local failure post-radiation for posterior uveal melanoma should be retreated either by enucleation or re-treatment by brachytherapy.\textsuperscript{137} Most cases of failed local control primarily treated with radiation are enucleated.

Charged-particle EBRT (i.e., protons, carbon ions, or helium ions), and photon-based radiosurgery (i.e., linear accelerator, gammaknife, or cyberknife) have also been used in the setting of uveal melanoma. Proton beam RT carries a local control rate of 93.9% at 5 years and 92.1% at 10 years.
The ocular conservation rates were 91.1% at 5 years and 87.3% at 10 years.\textsuperscript{138} Similar results have been reported elsewhere.\textsuperscript{139-144}

**Adjuvant Therapies**

**Transpupillary Thermotherapy (TTT).** TTT uses an infrared laser through a dilated pupil and is not typically used as a primary treatment for uveal melanoma anymore due to high recurrence rates. It is now most commonly used as an adjuvant treatment to RT or as treatment of medium risk nevi/indeterminate lesions. Due to its penetrance limitations, this therapy is best suited for small (1.0-3.0 mm in apical height and 5.0-16.0 mm largest basal diameter) melanomas.\textsuperscript{23} A randomized controlled trial among patients with small choroidal melanomas (N=95) compared TTT primary therapy with brachytherapy and found, after a mean follow-up of 56.2 months (range, 24-118 months; standard deviation [SD], 22.6), that tumour regression occurred in 45 patients (92%) in the TTT group versus 45 patients (98%) in the brachytherapy group (p=0.397). Recurrences developed in four TTT patients and one brachytherapy patient.\textsuperscript{61}

A retrospective case-matched comparative study (N=36) and retrospective observational study (N=21) were conducted in parallel to compare TTT alone vs. TTT plus plaque RT. Local failure occurred in six patients (29%) and was associated with an increased number of TTT spots per session (p=0.023) and decreased tumour pigmentation (p=0.001). The RT plus TTT group regressed rapidly, with no local failures. No patient developed metastasis. TTT performed as a supplemental therapy in RT-resistant tumours (6 patients) or tumours at high risk for local failure with RT alone (3 patients) successfully induced tumour shrinkage and resolution of exudative retinal detachment in all 6 tumours RT-resistant tumours and after a mean follow-up of 32 months (range, 10–52 months), all 9 tumours regressed satisfactorily, with no local failures or enucleations.\textsuperscript{62}

**Intra-vitreal Anti-Vascular Endothelial Growth Factor (VEGF) Medications.** One of the major causes of visual loss in patients who have received RT is radiation retinopathy and optic neuropathy. The main underlying cause of this visual loss is vascular damage leading to both ischemia from capillary drop out and exudation from vascular injury and ischemia.\textsuperscript{145} Similarly, one of the primary causes of enucleation post RT is neovascularization that occurs secondary to ischemia and VEGF production leading to uncontrolled neovascular glaucoma. Anti-VEGF agents have been developed and utilized to suppress the vascular permeability and neovascularization process that can result in significant ocular morbidity. Multiple case series have shown substantial reductions of subretinal fluid, intra-retinal hemorrhages, visible retinal infarcts, regression of neovascularization, and improved visual function.\textsuperscript{67, 125, 146-152}

Adjuvant prophylactic intravitreal bevacizumab injections every 4 months for 2 years post plaque treatment significantly improved visual outcomes by reducing optical coherence tomography (OCT)-evident macular edema, clinically notable radiation maculopathy, moderate vision loss, and poor final visual acuity.\textsuperscript{147} Similarly the use of intravitreal anti-VEGF for symptomatic radiation retinopathy has also shown improvement in macular thickness and visual function.\textsuperscript{65-67, 70, 146, 148, 153, 154}
Systemic Adjuvant Treatments

No studies to date have shown any benefit from adjuvant therapy in reducing metastasis rates in patients at high risk for future metastasis (GEP class 2 and monosomy 3).

Management of Metastatic or Recurrent Disease.

Local treatment failure (ocular recurrence)

Local (ocular) recurrence is typically treated with enucleation or repeat brachytherapy. Some centers will utilize TTT for small recurrence at the margin of the tumour.62, 155, 156

Local therapy in the setting of limited metastatic disease

There are some data to suggest that resection of uveal melanoma liver metastases may prolong survival,157, 158 including a single-arm prospective study among twelve patients who were able to achieve a median recurrence free survival (RFS) of 19 months (6-78; 5-year RFS 15.6%) and an OS of 27 months (11-86; 5-year OS 53.3%) following complete resection.159 Retrospective data also suggest that resection of liver metastases is associated with a 3.7-fold increase in median survival, as compared to no surgery.100 Similar data have been reported elsewhere.101, 160, 161 However, the results of these non-comparative cohorts may be influenced by lead-time bias and/or favorable tumour biology in patients who are candidates for resection.23 In general, surgery is a preferred option in younger patients with large tumours and in patients with a metastasis. The option of surgery needs to be carefully considered due to risk of metastatic spread to remaining liver and systemically.

Surgical resection in combination with chemotherapy may offer some benefit to patients with metastatic disease. A prospective study of aggressive surgery (i.e., removal of as much liver disease as possible) and implantation of an intra-arterial catheter for delivery of chemotherapy (e.g., fotemustine and/or DTIC-platinum for 4–9 cycles) among patients with uveal melanoma metastatic to the liver (N=75) demonstrated complete resection in 27.5% and significant tumour reduction in 49.3%. Median OS was 10 months in patients who received complete treatment surgery plus chemotherapy; curative resection improved the median OS to 22 months (p<0.001).162 The use of chemotherapeutic agents listed above as systemic component of the combination is less than ideal given the potential benefits with systemic immunotherapy. Further study incorporating new agents, especially immunotherapeutic agents, will be of great interest. Clinical trial participation is encouraged.

Ablation. Ablative techniques (i.e., thermoablation104 and radiofrequency ablation105 and radioembolization102) have been used in the setting of metastatic uveal melanoma. Studies have shown prolonged survival when liver metastases are treated by either surgical resection and/or percutaneous ablation. Although liver resection remains the Gold Standard, thermal ablation has the advantage of sparing liver parenchyma as well as providing a minimally invasive outpatient procedure.163, 164

A retrospective review of the charts of eight patients with liver metastasis from ocular melanoma who underwent surgery and/or radiofrequency ablation at the University of Southern California revealed
that four patients had all metastatic liver lesions addressed: one patient underwent left lateral segmentectomy and three patients had combinations of left lateral segmentectomies, wedge resections and radiofrequency ablation of two to four lesions. The median survival of patients who underwent surgery alone or in conjunction with radiofrequency ablation to address all liver lesions was 46 months. In a phase II trial of radioembolization for the treatment of uveal melanoma hepatic metastasis, treatment-naïve patients (n=24) achieved a median OS of 18.5 months with a 1-year survival of approximately 61%. Participants treated with radioembolization in whom prior immunoembolization treatment failed (n=23) achieved a median OS of 19.2 months with a 1-year survival of approximately 70%. Grade 3 treatment-related toxicities were reported in three of the treatment-naïve patients and in one of the patients who received prior immunoembolization. These results suggest that radioembolization is safe and effective first- or second-line treatment in this setting.

**Advanced metastatic recurrence**

Systemic therapies for metastatic uveal melanoma have been largely modeled after therapies for cutaneous melanoma. In the pre-immunotherapy era, phase II chemotherapy data did not demonstrate clinical efficacy in metastatic uveal melanoma with any of the tested single agents or combinations of agents. However, the use of immune checkpoint inhibitors, either singly or in combination, has demonstrated more promising results, and a recently reported phase III randomized clinical trial supports the use of immunotherapy for the treatment of patients with unresectable metastatic disease. Clinical trials for the uveal melanoma patient population are emerging, and where possible enrolment in a clinical trial is recommended.

**Chemotherapy.** Systemic chemotherapy alone for the management of metastases or recurrent disease is largely ineffective, and therefore not recommended. Clinical trials have tested the efficacy of carboplatin, paclitaxel, docosahexaenoic acid-paclitaxel, and cisplatin by transarterial chemoembolization (TACE). Of these, the most efficacious therapy was cisplatin TACE, with a partial response of 57%. None of the regimens were able to achieve a complete response in any patients. A complete summary of phase II data is in Appendix B.

**Immunotherapy.** Immunotherapies have demonstrated prolonged survival in patients with metastatic cutaneous melanoma. Ipilimumab, an anti-CTLA4 antibody, have demonstrated activity in patients with advance uveal melanoma in retrospective and expanded access studies. These reports varied in inclusion, exclusion, treatment protocols, and reported highly variable outcomes making the summary data problematic. Yet if we summarize, these six reports in, 188 patients with advanced uveal melanoma have been treated with ipilimumab with one complete response, 7 partial responses, and 52 patients with stable disease. This translates to a response rate of 4.3% and disease control rate of 31.9%. The tumour kinetics and response patterns in these patients with uveal melanoma were similar to those with cutaneous melanoma treated with ipilimumab. This response rate seen in patients with ocular melanoma would appear to be lower than that reported in the phase III cutaneous melanoma trials of ipilimumab alone or combined with dacarbazine of 10.9% and 15.2%, respectively.
It is hypothesized that metastatic uveal melanoma is less responsive to immune checkpoint inhibitor due to the presence of fewer somatic mutations, which results in fewer potential neoantigens that can be targeted by antitumour immunity. Additionally, the liver as an immune-modulatory organ may protect uveal melanoma metastases from immune surveillance.\textsuperscript{172} However, uveal melanoma expresses several immunogenic antigens, such as glycoprotein 100 (gp100), melanoma antigen recognized by T cells 1 (MART-1), and tyrosinase, and a subset of uveal melanoma are able to elicit a vigorous immune response.\textsuperscript{173} Rare, marked response to immunotherapy has been reported in uveal melanoma, and molecular investigation of these tumours revealed high tumour mutation burden (TMB) secondary to germline, loss-of function MBD4 mutations.\textsuperscript{174, 175} Johansson et al. recently demonstrated that iris uveal melanoma is unique among uveal melanoma subtypes in that it demonstrates ultraviolet radiation-associated DNA damage, and like MBD4-deficient tumours, has a high TMB.\textsuperscript{10} This suggests that metastatic iris uveal melanoma may be more likely to respond to immunotherapy than other variants of uveal melanoma, the vast majority of which have low TMB.

Wessely et al.\textsuperscript{176} recently reviewed the evidence for immune checkpoint inhibitors (ICI) in treating metastatic uveal melanoma. Among nine prospective and retrospective studies using anti-CTLA-4 (ipilimumab or tremelimumab) for the treatment of metastatic uveal melanoma, the largest prospective observational study with 53 patients reported ORR of 0% and a median OS of 6.8 months. The largest retrospective study with 82 patients reported ORR of 4.8% and a median OS of 6.0 months. Among 11 retrospective and prospective studies utilizing anti-PD1 agents (pembrolizumab or nivolumab), the largest prospective study had 34 evaluable patients and reported ORR of 5.8% and median OS of 11 months for patients on nivolumab. The largest retrospective study which followed 43 patients on pembrolizumab reported ORR of 7.0% and a median OS of 10.3 months. Improved responses are reported with combination CTLA-4/PD-1 ICI. One retrospective study consisting of 64 patients reported ORR of 15.6% (3.1% CR) and a median OS of 16.1 months,\textsuperscript{177} while another with 89 patients reported ORR of 11.0% (1% CR) and a median OS of 15.0 months.\textsuperscript{178} Bol et al. reported the longest median OS in the literature at 18.9 months for combination ipilimumab and nivolumab, with an ORR of 21.0%, albeit with a small sample size of 19 patients.\textsuperscript{179} A recent study by Klemen et al. followed 30 metastatic uveal melanoma patients treated with ICI. The study had four patients survive >5 years, all of whom received anti-CTLA-4 and anti-PD1, either sequentially or in combination. The author suggested that exposure to ipilimumab in addition to anti-PD1 may be integral in achieving long-term survival in metastatic uveal melanoma.\textsuperscript{180} Collectively, data suggest that combined ICI may be superior to anti-PD1 or anti-CTLA-4 monotherapy, although limitations in the current data (including small sample sizes, potential selection bias, and a lack of clinical trials with comparative study design) must be noted.

More robust data supporting the use of ICI for metastatic uveal melanoma is emerging. Nivolumab and pembrolizumab both demonstrate activity in prospective, non-comparative phase II clinical trials,\textsuperscript{78, 79} and a single-arm phase II clinical trial utilizing the combination of nivolumab with ipilimumab resulted in an objective response rate of 18%, and median OS of nearly two years.\textsuperscript{77}
Most recently, data from a randomized phase III clinical trial confirms a survival advantage for HLA-A*02:01 positive adult patients treated with the novel immunotherapy tebentafusp, a novel bispecific protein comprised of a soluble T cell receptor fused to an anti-CD3 immune-effector function (clinicaltrials.gov identifier: NCT03070392). When compared against investigator’s choice of therapy (including ipilimumab, pembrolizumab or dacarbazine chemotherapy), treatment with tebentafusp improved OS (HR 0.51) with a one-year OS rate of 73% and median OS of 22 months.

**Molecularly targeted agents.** Greater than 80% of primary uveal melanomas carry active mutations in the GNAQ or GNA11 genes, which encode for G protein alpha subunits, leading to activation of the mitogen-activated protein kinase (MEK) pathway. Advancements in our understanding of the molecular and genetic mechanisms of pathophysiology has generated interest in the use of receptor tyrosine kinase inhibitors, including the MEK inhibitors selumetinib and trametinib, and the c-KIT (CD117) inhibitor sunitinib. Invariably resistance to these agents develops in a matter of months. While modest clinical activity with the use of these agents has been reported, none have yet been shown to improve OS. Clinicians and patients who decide to use targeted therapies in the metastatic setting should understand that treatment-related toxicities may be significant and a detriment to the quality of life.

**Follow-Up**

There are no high-level data to inform the most appropriate way to monitor patients who have undergone treatment for uveal melanoma. As such, there is no consensus within the ophthalmic or oncologic community regarding the role of surveillance for detection of metastases in these patients. Some lower-level data are available on the usefulness of specific imaging tests and biochemical tests in the detection of metastasis. Since surgical resection, ablation therapy and/or systemic immunotherapy evidence has suggested improved survival, most ocular oncology centers perform rigorous follow-up on high-risk patients.

Liver function tests are not sufficiently sensitive to be used as a sole method of surveillance. Regarding liver function tests (LFTs), an Israeli study among 30 uveal melanoma patients with metastases and 80 non-metastatic controls looked retrospectively at the use of LFTs and liver imaging in detecting metastases. At the time of diagnosis of liver metastases by imaging, only 50% of patients had at least one abnormal LFT (vs. 5% of controls). Alkaline-phosphatase and lactate dehydrogenase were the most predictive tests. Lactate dehydrogenase and aspartate-aminotransferase were predictive at 80% of the upper normal limit, whereas alkaline-phosphatase and gamma-glutamyltransferase were most predictive at the upper normal limit.

Clinical characteristics and tumour genetics predict survival. Therefore, a customized follow-up routine, based on the risk category of the patient is recommended. Ultrasound (U/S) has demonstrated high specificity (i.e., 100%) but low sensitivity (i.e., 14%) for the detection of uveal melanoma liver metastases. The use of U/S in the follow-up of high-risk patients should therefore complement other more sensitive tests. Several studies have looked at the use of various imaging modalities in detecting metastases, particularly in the liver, at follow-up. MRI offers
consistently good sensitivity (92-96%), while that of PET-CT is variable (35-100%). In a head-to-head comparison of MRI and PET-CT, sensitivity was higher with MRI (67% vs. 41%; p=0.01), while positive predictive value was slightly higher with PET-CT (95% vs. 100%; p=0.01); the authors concluded that MRI was superior to PET-CT for detecting liver metastases from uveal melanoma. In a cohort of 188 high-risk patients, 6-monthly MRI of the abdomen detected metastases before symptoms in 92% of patients, resulting in 14% of patients who qualified for liver resection. Consensus-based guidelines recommend that follow-up consist of annual history and physical exam, LFTs, PET-CT or MRI of the abdomen, CXR, and liver U/S. High-risk patients require more frequent imaging. To date there is no data on the impact of follow-up on survival.

Low-risk patients (i.e., GEP class 1a/1b; no monosomy 3 detected; or tumour ≤9 mm thick and no genetic assessment) should undergo liver U/S and physical exam annually, for up to 10 years; follow-up may be transitioned to the family physician at 5 years. High-risk patients (i.e., GEP class 2; monosomy 3 detected; or tumour ≥9 mm thick and no genetic assessment) should undergo physical exam annually, indefinitely, plus imaging every six months consisting of a liver U/S alternating with abdominal/liver MRI for 10 years. If body habitus limits U/S, consideration for other modalities should be given. Follow-up may be transitioned to the family physician at 5-10 years.

There have been several reports of an increased risk of cutaneous melanoma following a diagnosis of uveal melanoma. The risk varies significantly between studies and may be partially related to increased surveillance. At present there is insufficient evidence to recommend universal screening for cutaneous melanoma of these individuals. In select individuals (those with significant risk factors for cutaneous melanoma) consider referral to a dermatologist for baseline total skin examination. Anecdotally, follow-up assessments have typically consisted of history and physical exam, liver function studies, PET-CT or MRI of the chest and abdomen and/or CXR and liver U/S. These assessments are typically performed annually, except in the case of patients with monosomy 3 or GEP class 2, who should undergo liver U/S every 3 months due to the increased risk of metastases.
Figure 2. Kaplan-Meier survival analysis in 50 uveal melanoma patients. Molecular class indicates class label using the gene expression signature. Pathology indicates the predominant tumor cell type indicated on the official pathology report. Other clinical features are indicated. All deaths were due to melanoma metastasis. Statistical significance is indicated for each parameter. Reproduced with permission from Onken M et al. Cancer Res 2004.
### Table 3. Accuracy of various imaging modalities in the detection of uveal melanoma metastases

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Modality</th>
<th>Metastases Site</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive Predictive Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marshall, 2013&lt;sup&gt;99&lt;/sup&gt;</td>
<td>MRI</td>
<td>liver</td>
<td>92%</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Orcurto, 2012&lt;sup&gt;116&lt;/sup&gt;</td>
<td>MRI PET-CT</td>
<td>liver</td>
<td>96%</td>
<td>35%</td>
<td>n/a n/a</td>
</tr>
<tr>
<td>Freton, 2012&lt;sup&gt;192&lt;/sup&gt;</td>
<td>PET-CT (whole body)</td>
<td>Any</td>
<td>n/a</td>
<td>94%</td>
<td>100%</td>
</tr>
<tr>
<td>Klingenstein, 2010&lt;sup&gt;185&lt;/sup&gt;</td>
<td>PET-CT (whole body)</td>
<td>liver or lung</td>
<td>100%</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Servois, 2010&lt;sup&gt;115, 116&lt;/sup&gt;</td>
<td>MRI PET</td>
<td>liver</td>
<td>67%</td>
<td>45%</td>
<td>95% 100%</td>
</tr>
<tr>
<td>Francken, 2006&lt;sup&gt;114&lt;/sup&gt;</td>
<td>PET</td>
<td>liver</td>
<td>100%</td>
<td>67%</td>
<td>88%</td>
</tr>
<tr>
<td>Finger, 2005&lt;sup&gt;33&lt;/sup&gt;</td>
<td>PET (whole body)</td>
<td>Any</td>
<td>100%</td>
<td>94%</td>
<td>100%</td>
</tr>
<tr>
<td>Semelka, 2001&lt;sup&gt;187&lt;/sup&gt;</td>
<td>MRI CT</td>
<td>liver</td>
<td>n/a</td>
<td>n/a</td>
<td>98% 75%</td>
</tr>
<tr>
<td>Eskelin, 1998&lt;sup&gt;188&lt;/sup&gt;</td>
<td>AST ALT AP LDH</td>
<td>liver</td>
<td>43% 38% 27% 67%</td>
<td>93% 90% 95% 96%</td>
<td>62% 68% 77% 35%</td>
</tr>
<tr>
<td>Hicks, 1998&lt;sup&gt;113&lt;/sup&gt;</td>
<td>CXR U/S AST AP</td>
<td>any</td>
<td>1.8% 14% 15% 25%</td>
<td>100% 100% 89% 86%</td>
<td>100% 100% 28% 33%</td>
</tr>
</tbody>
</table>
References


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### Appendix A: Uveal Melanoma TNM Staging (modified from the AJCC 8th Edition)

**Table 1. Primary Tumour Definitions**

<table>
<thead>
<tr>
<th>Iris</th>
<th>Ciliary Body and Choroid</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T</strong>x</td>
<td>Primary tumour cannot be assessed</td>
</tr>
<tr>
<td><strong>T</strong>0</td>
<td>No evidence of primary tumour</td>
</tr>
<tr>
<td><strong>T</strong>1</td>
<td>Tumour limited to the iris</td>
</tr>
<tr>
<td><strong>T</strong>1a</td>
<td>Tumour limited to the iris; ≤3 clock hours in size</td>
</tr>
<tr>
<td><strong>T</strong>1b</td>
<td>Tumour limited to the iris; &gt;3 clock hours in size</td>
</tr>
<tr>
<td><strong>T</strong>1c</td>
<td>Tumour limited to the iris with secondary glaucoma</td>
</tr>
<tr>
<td><strong>T</strong>1d</td>
<td>Tumour confluent with or extending into the ciliary body, choroid, or both</td>
</tr>
<tr>
<td><strong>T</strong>2</td>
<td>Tumour confluent with or extending into the ciliary body, choroid, or both, without secondary glaucoma</td>
</tr>
<tr>
<td><strong>T</strong>2a</td>
<td>Tumour confluent with or extending into the ciliary body without secondary glaucoma</td>
</tr>
<tr>
<td><strong>T</strong>2b</td>
<td>Tumour confluent with or extending into the ciliary body and choroid, without secondary glaucoma</td>
</tr>
<tr>
<td><strong>T</strong>2c</td>
<td>Tumour confluent with or extending into the ciliary body, choroid, or both, with secondary glaucoma</td>
</tr>
<tr>
<td><strong>T</strong>2d</td>
<td>Tumour confluent with or extending into the ciliary body, choroid, or both, with scleral extension</td>
</tr>
<tr>
<td><strong>T</strong>3a</td>
<td>Tumour with extrascleral extension</td>
</tr>
<tr>
<td><strong>T</strong>3b</td>
<td>Tumour with extrascleral extension ≤5 mm in largest diameter</td>
</tr>
<tr>
<td><strong>T</strong>3c</td>
<td>Tumour with extrascleral extension &gt;5 mm in largest diameter</td>
</tr>
<tr>
<td><strong>T</strong>3d</td>
<td>Tumour with extrascleral extension</td>
</tr>
<tr>
<td><strong>T</strong>4a</td>
<td>Tumour with extrascleral extension without ciliary body involvement and extraocular extension</td>
</tr>
<tr>
<td><strong>T</strong>4b</td>
<td>Tumour with extrascleral extension</td>
</tr>
<tr>
<td><strong>T</strong>4c</td>
<td>Tumour with extrascleral extension without ciliary body involvement and extraocular extension</td>
</tr>
<tr>
<td><strong>T</strong>4d</td>
<td>Tumour with extrascleral extension without ciliary body involvement and extraocular extension</td>
</tr>
</tbody>
</table>

Last revision: June 2021
Iris Ciliary Body and Choroid

**T4e**

Any tumour size category with extraocular extension >5 mm in largest diameter

**Notes for Iris Melanomas:**

- Originate from, and are predominately located in, this region of the uvea. If less than half the tumour volume is located within the iris, the tumour may have originated in the ciliary body, and consideration should be given to classifying it accordingly.

**Notes for Primary Ciliary Body and Choroidal Melanomas:**

- Classified according to the four tumour size categories defined in figure entitled "Classification for ciliary body and choroid uveal melanoma based on thickness and diameter."
- In clinical practice, the largest tumour basal diameter may be estimated in optic disc diameters (DD; average: 1 DD = 1.5 mm), and tumour thickness may be estimated in diopters (average: 2.5 diopters = 1 mm). Ultrasoundography and fundus photography are used to provide more accurate measurements.
- When histopathologic measurements are recorded after fixation, tumour diameter and thickness may be underestimated because of tissue shrinkage.

### Table 2. Classification for Ciliary Body and Choroid Uveal Melanoma Based on Thickness and Diameter

<table>
<thead>
<tr>
<th>Thickness (mm)</th>
<th>≤3.0</th>
<th>3.1 to 6.0</th>
<th>6.1 to 9.0</th>
<th>9.1 to 12.0</th>
<th>12.1 to 15.0</th>
<th>15.1 to 18.0</th>
<th>&gt;18.0</th>
</tr>
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<tbody>
<tr>
<td>&gt;15.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>12.1 to 15.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9.1 to 12.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6.1 to 9.0</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3.1 to 6.0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>≤3.0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>4</td>
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</table>

### Table 3. Regional Lymph Nodes (N) Definitions

<table>
<thead>
<tr>
<th>N</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node involvement</td>
</tr>
<tr>
<td>N1</td>
<td>Regional lymph node metastases or discrete tumour deposits in the orbit</td>
</tr>
<tr>
<td>N1a</td>
<td>Metastasis in one or more regional lymph node(s)</td>
</tr>
<tr>
<td>N1b</td>
<td>No regional lymph nodes are positive, but there are discrete tumour deposits in the orbit that are not contagious to the eye (choroidal and ciliary body)</td>
</tr>
</tbody>
</table>

### Table 4. Distant Metastasis (M) Definitions

<table>
<thead>
<tr>
<th>M</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>No distant metastases by clinical classification</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
<tr>
<td>M1a</td>
<td>Largest diameter of the largest metastasis ≤3 cm</td>
</tr>
<tr>
<td>M1b</td>
<td>Largest diameter of the largest metastasis 3.1–8.0 cm</td>
</tr>
<tr>
<td>M1c</td>
<td>Largest diameter of the largest metastasis ≥8.1 cm</td>
</tr>
</tbody>
</table>
Table 5. TNM Stage Definitions

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
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<tr>
<td>I</td>
<td>T1a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIA</td>
<td>T1b-d</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T2a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIB</td>
<td>T2b</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIIA</td>
<td>T2c-d</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3b-c</td>
<td>N0</td>
<td>M0</td>
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<td>T4a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIIB</td>
<td>T3d</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T4b-c</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIIIC</td>
<td>T4d-e</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IV</td>
<td>Any T</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>Any T</td>
<td>Any N</td>
<td>M1a-c</td>
</tr>
</tbody>
</table>
## Appendix B: Evidence for Systemic Therapy in Advanced Uveal Melanoma

<table>
<thead>
<tr>
<th>Author (trial), Year</th>
<th>Design</th>
<th>Treatments</th>
<th>Patients (n)</th>
<th>Response</th>
<th>Survival</th>
<th>Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bhatia</strong>&lt;br&gt;(SWOG S0512), 2012&lt;sup&gt;82&lt;/sup&gt;</td>
<td>phase II</td>
<td>carboplatin (AUC 6) + paclitaxel (225 mg/m²) IV on day 1 plus sorafenib (400 mg) PO twice daily x 6</td>
<td>stage IV uveal melanoma w/ 0-1 prior systemic therapy (n=25)</td>
<td>overall: 0% (95% CI 0-14%)</td>
<td>PFS (med): 4 mos (95% CI 1-6 mos)</td>
<td>PFS (6-mos): 29% (95% CI 13%-48%)</td>
</tr>
<tr>
<td><strong>Mahipal</strong>, 2012&lt;sup&gt;83&lt;/sup&gt;</td>
<td>phase II</td>
<td>sunitinib malate (37.5 mg/d continuously) 4-week cycles 2nd line in 17/20 pts</td>
<td>metastatic uveal melanoma expressing c-kit (n=20)</td>
<td>partial: 1 patient</td>
<td>OS (med): 8.2 mos</td>
<td>fatigue: 90% diarrhea: 60% hemorrhage: 55% anorexia: 45% hand-foot syndrome: 25% hypothyroidism: 25% rash: 25%</td>
</tr>
<tr>
<td><strong>Homsi</strong>, 2010&lt;sup&gt;84&lt;/sup&gt;</td>
<td>phase II</td>
<td>Docosahexaenoic acid (DHA)-paclitaxel (500 mg/m²/week) IV for 5 weeks (6-week cycles)</td>
<td>metastatic uveal melanoma chemo-naive or previously treated (n=22)</td>
<td>stable disease: 32%</td>
<td>OS (med): 9.8 mos</td>
<td>neutropenia: 23% musculoskeletal pain: 10%</td>
</tr>
<tr>
<td><strong>Huppert</strong>, 2010&lt;sup&gt;85&lt;/sup&gt;</td>
<td>phase II</td>
<td>cisplatin (100mg/m₂) by transarterial chemoembolization (TACE) carboplatin in 3/14 pts due to kidney function</td>
<td>metastatic uveal melanoma; liver mets (n=14)</td>
<td>partial: 8 patients (57%) stable disease: 4 patients (29%) progression: 2 patients (14%) (med time to progression: 8.5 mos)</td>
<td>OS (med): 11.5 mos (3-69)</td>
<td>subgroup analysis (mets &lt;25% vs. ≥25%): 17 vs. 11 mos (p=0.18)</td>
</tr>
<tr>
<td><strong>Fiorentini</strong>, 2009&lt;sup&gt;86&lt;/sup&gt;</td>
<td>phase II</td>
<td>transarterial chemoembolization (TACE) beads preloaded with irinotecan (100 mg)</td>
<td>metastatic uveal melanoma; liver mets (n=10)</td>
<td>objective response: 100% partial response: 10</td>
<td>med f/u 6.5 mos</td>
<td>abdominal pain</td>
</tr>
<tr>
<td><strong>van Iersel</strong>, 2008&lt;sup&gt;193&lt;/sup&gt;</td>
<td>phase II</td>
<td>hyperthermic IHP with melphalan (200 mg)</td>
<td>melanoma with liver mets (n=18; 12 had uveal melanomas)</td>
<td>uveal melanoma patients: partial response: 4 pts stable disease: 6 pts progressive: 2 pts</td>
<td>DFS (med): 6.6 mos OS (med): 10.0 mos</td>
<td>no treatment-related mortality grade 3-4 hepatotoxicity: 10 pts (56%) veno-occlusive disease: 4 pts</td>
</tr>
<tr>
<td><strong>O’Neill</strong>, 2006&lt;sup&gt;87&lt;/sup&gt;</td>
<td>phase II</td>
<td>dacarbazine (850 mg/m²) plus treosulfan (8 g/m²) q 3 weeks for a max of 6 cycles (1st line)</td>
<td>metastatic uveal melanoma (n=15)</td>
<td>overall: none stable disease: 2 patients</td>
<td>DFS (med): 12 weeks OS (med): 30 weeks</td>
<td>major toxicities were hematological (particularly thrombocytopenia)</td>
</tr>
<tr>
<td><strong>Schmittel</strong>, 2006&lt;sup&gt;89, 91&lt;/sup&gt;</td>
<td>phase II</td>
<td>1. gemcitabine (1000 mg/m²) + treosulfan 2. treosulfan alone (3500 mg/m²)</td>
<td>metastatic uveal melanoma chemo-naive (n=48)</td>
<td>stable disease: 7 patients in gem-T group vs. 3 patients in</td>
<td>PFS (med): 3 mos (95% CI 1.1-4.9) for gem-T vs. 2 mos (95% CI 1.7-2.3) for T (p=.008)</td>
<td>grade 3-4: leukopenia: 4 gem-T vs. 0 T nausea: 3 gem-T vs. 3 T</td>
</tr>
<tr>
<td>Author (trial), Year</td>
<td>Design</td>
<td>Treatments</td>
<td>Patients (n)</td>
<td>Response</td>
<td>Survival</td>
<td>Adverse Events</td>
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<tr>
<td>Patel, 2005&lt;sup&gt;90&lt;/sup&gt;</td>
<td>phase II</td>
<td>1,3-bis(2-chloroethyl)-1-nitroso urea (BCNU) dissolved in ethiodized oil for hepatic artery chemoembolization</td>
<td>metastatic uveal melanoma; mets to liver (n=24)</td>
<td>complete response: 1 patient partial response: 4 patients stable disease: 13 patients</td>
<td>PFS (12-mos): 16.7% for gem-T vs. 0% for T PFS (6 mos): 34.8% for gem-T vs. 17.9% for T</td>
<td>FN: 2 gem-T vs. 0 T</td>
</tr>
<tr>
<td>Schmidt-Hieber, 2004&lt;sup&gt;88&lt;/sup&gt;</td>
<td>phase II</td>
<td>bendamustine (120 mg/m² days 1 and 2) q 3 weeks</td>
<td>metastatic uveal melanoma; progression during or after 1st line chemo (n=11)</td>
<td>progressive disease: all 11 pts</td>
<td>n/a</td>
<td>grade 3-4: anemia (2 pts), thrombocytopenia (1 pt), leukocytopenia (2 pts)</td>
</tr>
<tr>
<td>Agarwala, 2004&lt;sup&gt;92&lt;/sup&gt;</td>
<td>phase II</td>
<td>cisplatin (100 mg/m² starting; increased in 25% increments to a max 125 mg/m²)</td>
<td>metastatic uveal melanoma; liver mets (n=19)</td>
<td>overall response rate: 16%</td>
<td>n/a</td>
<td>any: renal, hepatic and hematological</td>
</tr>
<tr>
<td>Alexander, 2003&lt;sup&gt;93, 165&lt;/sup&gt;</td>
<td>phase II</td>
<td>hyperthermic IHP with melphalan (1.5 mg/kg; mean total 105 mg)</td>
<td>metastatic ocular melanoma; liver mets (n=29)</td>
<td>complete response: 3 pts (10%), lasting 12-15 mos partial response: 15 pts (52%), lasting 10 mos (mean)</td>
<td>med f/u: 30.7 mos PFS (med): 8.0 mos OS (med): 12.1 mos</td>
<td>NR</td>
</tr>
<tr>
<td>Kivela, 2003&lt;sup&gt;94&lt;/sup&gt;</td>
<td>phase II</td>
<td>bleomycin, vincristine, lomustine, dacarbazine q4 w x 2 cycles + IFN alpha-2b (3 x 10⁶ IU)</td>
<td>metastatic uveal melanoma (n=24)</td>
<td>objective response: 0% stable disease: 2 pts (8.3%) progression: 20 pts</td>
<td>PFS (med): 1.9 mos (95% CI: 1.8-3.4 mos) OS (med): 10.6 mos (95% CI: 6.9-16.4 mos)</td>
<td>grade 3: alopecia and neurotoxicity in 13% of pts</td>
</tr>
<tr>
<td>Bedikian, 2003&lt;sup&gt;95&lt;/sup&gt;</td>
<td>phase II</td>
<td>temozolomide (75 mg/m² per day orally for 21 days) q 4 weeks</td>
<td>metastatic choroidal melanoma (n=14)</td>
<td>complete response: none partial response: none stable disease: 2 pts</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Pyrhonen, 2002&lt;sup&gt;96&lt;/sup&gt;</td>
<td>phase II</td>
<td>bleomycin, vincristine, dacarbazine, lomustine q 4 weeks plus IFN (3 x 10⁶ IU)</td>
<td>metastatic uveal melanoma; liver mets (stage IVB; n=20)</td>
<td>partial response: 3 (15%; 95% CI 0-38) stable disease: 11 (55%; 95%)</td>
<td>stage IVBa: 17 mos (95% CI 4-37) stage IVBb: 11 mos (95% CI 1-23)</td>
<td>grade 3-4 hematologic toxicity, either leukopenia or thrombocytopenia</td>
</tr>
<tr>
<td>Author (trial), Year</td>
<td>Design</td>
<td>Treatments</td>
<td>Patients (n)</td>
<td>Response</td>
<td>Survival</td>
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</tr>
<tr>
<td>Becker, 2002&lt;sup&gt;97&lt;/sup&gt;</td>
<td>phase II</td>
<td>fotemustine (100 mg/m²) into hepatic artery or peripheral vein</td>
<td>metastatic ocular melanoma (n=48)</td>
<td>objective response: 21.7% for intra-arterial vs. 8% for peripheral vein</td>
<td>OS (med): 369 days for intra-arterial vs. 349 days for peripheral vein</td>
<td>n/a</td>
</tr>
</tbody>
</table>
Development and Revision History
This guideline was reviewed and endorsed by the Alberta Provincial Cutaneous Tumour Team. Members include [surgeons, oncologists, radiation oncologists, medical oncologists, dermatologists, nurses, pathologists, and pharmacists]. Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial Cutaneous Tumour Team, external participants identified by the Working Group Lead, and a methodologist from the Guideline Resource Unit. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Resource Unit Handbook.

This guideline was originally developed in July 2014. This guideline was revised in November 2014 and May 2021. Portions of this guideline have been published in Current Oncology.194

Levels of Evidence

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity</td>
</tr>
<tr>
<td>II</td>
<td>Small, randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity</td>
</tr>
<tr>
<td>III</td>
<td>Prospective cohort studies</td>
</tr>
<tr>
<td>IV</td>
<td>Retrospective cohort studies or case-control studies</td>
</tr>
<tr>
<td>V</td>
<td>Studies without control group, case reports, expert opinion</td>
</tr>
</tbody>
</table>

Strength of Recommendations

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>A</td>
<td>Strong evidence for efficacy with a substantial clinical benefit; strongly recommended</td>
</tr>
<tr>
<td>B</td>
<td>Strong or moderate evidence for efficacy but with a limited clinical benefit; generally recommended</td>
</tr>
<tr>
<td>C</td>
<td>Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, etc.); optional</td>
</tr>
<tr>
<td>D</td>
<td>Moderate evidence against efficacy or for adverse outcome; generally, not recommended</td>
</tr>
<tr>
<td>E</td>
<td>Strong evidence against efficacy or for adverse outcome; never recommended</td>
</tr>
</tbody>
</table>

Maintenance
A formal review of the guideline will be conducted in 2024. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

Abbreviations
AHS, Alberta Health Services; AJCC, American Joint Committee on Cancer; CBC, complete blood count; CCA, Cancer Care Alberta; CI, confidence interval; COMS, Collaborative Ocular Melanoma Study; CT, computed tomography; CXR, chest x-ray; EBRT, external beam radiotherapy; GEP, gene expression profile; gp100, glycoprotein 100; HR, hazard ratio; ICI, immune checkpoint inhibitor; 125I, Iodine-125; LFT, liver function test; MART-1, melanoma antigen recognized by T cells 1; MEK, mitogen-activated protein kinase; MLPA, multiplex ligation dependent probe amplification; MRI, magnetic resonance imaging; OCT, optical coherence tomography; ORR, overall response rate; OS, overall survival; 103Pd, Palladium-103; PET, positron emission tomography; RFS, recurrence free survival; RT, radiotherapy; 106Ru, Ruthenium-106; SD, standard deviation; TACE, transarterial chemoembolization; TMB, tumour mutation burden; TTT, transpupillary thermotherapy; UBM, ultrasound biomicroscopy; U/S, ultrasound; UV, ultraviolet; VEGF, vascular endothelial growth factor.

Disclaimer
The recommendations contained in this guideline are a consensus of the Alberta Provincial Cutaneous Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

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Conflict of Interest Statements
Dr. Ezekiel Weis (guideline lead) reports participation on the Castle Biosciences, Inc. Advisory Board (no financial remuneration or interest). Dr. Tina Cheng has nothing to disclose. Dr. Thomas Salopek has nothing to disclose. Dr. Claire Temple-Oberle has nothing to disclose. Dr. John Walker reports a relationship with Immunocore Pharmaceuticals as a participant in the randomized phase II clinical trial comparing tebentafusp against investigator’s choice for treatment of melanoma (NCT03070392). Brae Surgeoner has nothing to disclose.