UVEAL MELANOMA

Effective Date: November, 2014

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.

UVEAL MELANOMA

BACKGROUND

Melanoma of the uveal tract (i.e., iris, ciliary body, and choroid), sometimes referred to as 'ocular melanoma', is a rare form of cancer (Figure 1). It accounts for just 5% of all melanomas and occurs at an incidence rate of about 6 cases per million person years. [1,2] Nevertheless, melanoma is the most common primary intraocular malignancy in adults and is the second most common location for melanoma (second to the skin). The risk of developing uveal melanoma is higher in individuals of Caucasian race, light eye color, fair skin, have more cutaneous and iris nevi and freckles, and with a self-reported inability to tan. [3-7] Uveal melanoma typically only affects one eye. [3] Despite these specific similarities to cutaneous melanomas, the association between UV light and uveal melanoma has not been clarified. [5-7]

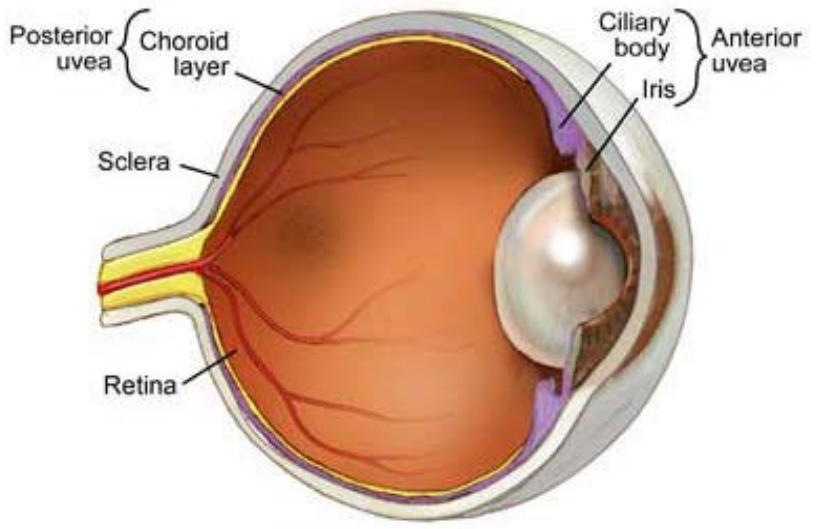

Figure 1. The choroid, ciliary body, and iris make up the uvea which contains the neural crest derived melanocyte and its associated malignant potential.

Uveal melanoma is a distinct clinical entity from other 'ocular' melanomas that can arise in the conjunctiva, the eyelid, and the orbit. [3] 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. [8,9] 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). [10,11] Mixed-cell type uveal melanoma (i.e., epithelioid and spindle) is the most common histological subtype of uveal melanoma and carries an intermediate prognosis. [11]

The five-year survival rate for uveal melanoma is 62% overall, 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. [8,9] Survival drops to 47% at 10 years and 25% at 20 years (Table 1). There is no successful treatment for metastatic disease yet. [12] The most common site of metastasis is the liver and the second most common is the lungs. The overall local recurrence rate following plaque brachytherapy is approximately 10% at five years (median 25.5 [12-71] months). [13]

Two modern prognostic tests requiring tumour sampling are currently available, including assessment of monosomy 3 status (monosomy portends a worse prognosis) and gene expression profiling. These are typically performed through a fine needle aspirate of the tumor at the time of definitive surgical treatment. Monosomy 3 is found in approximately 50% of patients and is associated with worse disease-free survival. [14-16] The estimated 3-year metastasis-free survival for patients with monosomy 3 is about 53%. [17] Due to the better biopsy yields and stronger evidence on prognostication, in Alberta the commercially available gene expression profile is now utilized instead of monosomy 3 testing. [17] The three signature classes of the gene expression profile are 1A, 1B, and 2. Signature class 2 carries a similar prognosis to monosomy 3 (Table 2). Gene expression profile, which is normally performed through a fine needle aspiration biopsy, is currently the most reliable predictive test for metastatic death (Figure 2, page 4). Data show that the strongest predictors of survival in patients with uveal melanoma are molecular class (i.e., class 2 is significantly worse than class 1; p=0.01), tumour location (i.e., anterior is significantly worse than posterior; p=0.01), and patient age (i.e., >60 years is significantly worse than <60 years; p=0.01). [17]

Table 1. Long-term survival estimates associated with uveal melanoma. [18,19]

Survival Measure	5-year	10-year	15-year	20-year	25-year
All-Cause Survival	62%	47%	35%	25%	21%
Melanoma Metastasis-Free Survival	69%	60%	55%	52%	51%
Second Cancer-Free Survival	95%	89%	85%	79%	76%

Table 2. Metastasis-free survival by signature class (i.e., gene expression profile). [18,1916]

Signature Class	Metastasis-Free Survival	
	3-year	5-year
1A	98%	98%
1B	93%	79%
2	50%	28%

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. [20,21]

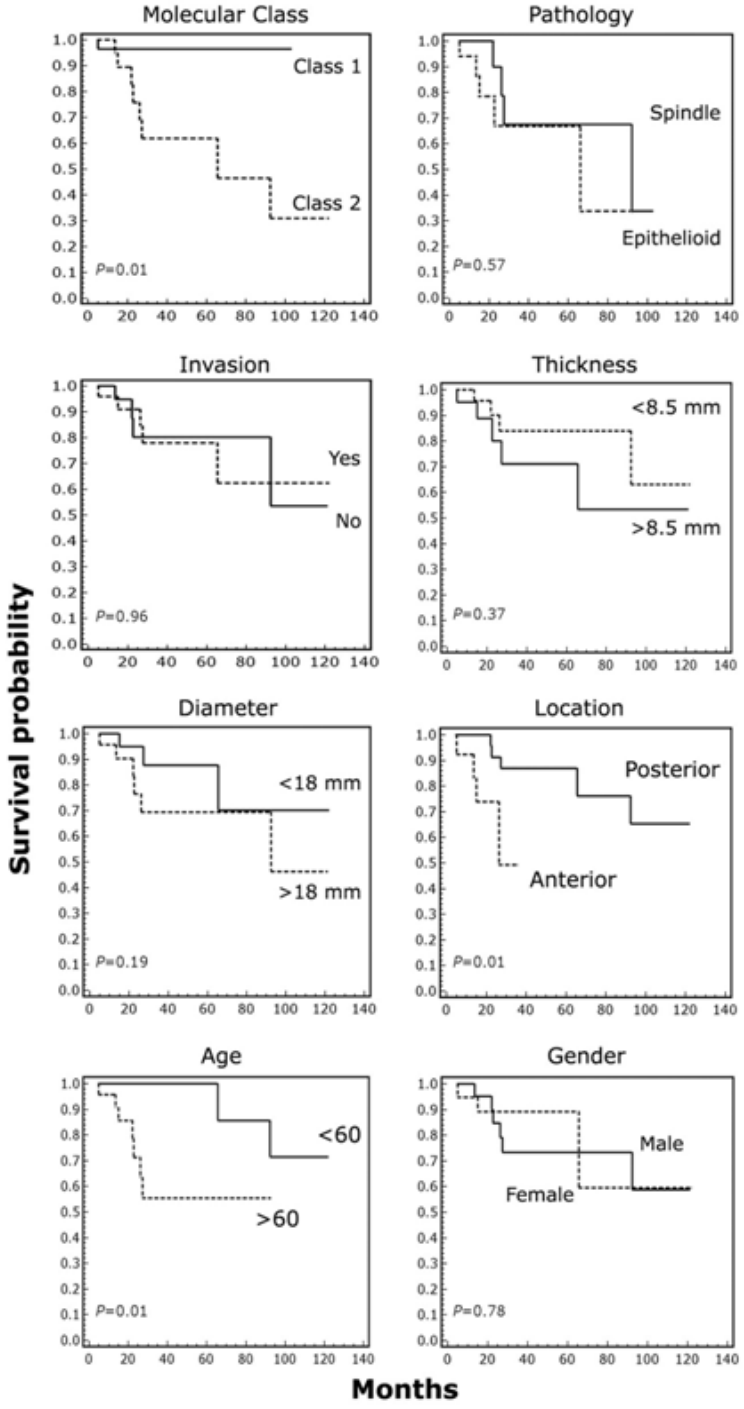

Figure 2. Kaplan-Meier survival analysis in 50 uveal melanoma patients. Molecular class indicates class label using the gene expression signature. Pathology indicates the predominant tumor cell type indicated on the official pathology report. Other clinical features are indicated. All deaths were due to melanoma metastasis. Statistical significance is indicated for each parameter. Reproduced with permission from *Onken M et al. Cancer Res 2004.*

GUIDELINE QUESTIONS

- How should patients with uveal melanoma be staged at baseline?
- How should uveal melanoma be managed?
- What follow-up testing is required for uveal melanoma patients?

DEVELOPMENT

This guideline was reviewed and endorsed by the Provincial Medical Lead of the Alberta Ocular Brachytherapy Program and Alberta Provincial Cutaneous Tumour Team. Members of the Alberta Provincial Cutaneous Tumour Team include ophthalmologists, general surgeons, plastic surgeons, dermatologists, medical oncologists, radiation oncologists, nurses, pathologists, and pharmacists. Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial Cutaneous Tumour Team and a methodologist from the Guideline Resource Unit (GURU). A detailed description of the methodology followed during the guideline development process can be found in the GURU handbook.

This guideline was originally developed in July, 2014. This guideline was revised in November, 2014.

SEARCH STRATEGY

The PUBMED database was searched (2000 through 2013 July) for phase II and III clinical trials, meta-analyses, and guidelines. Search terms included: “uveal melanoma” or “ocular melanoma” or “intraocular melanoma” with limits of studied in humans and English language publications. 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. A total of 16 phase II trials on systemic therapy (Appendix B) were returned from the search and deemed relevant. Six publications on proton beam therapy, six publications on brachytherapy, and ten publications on radiosurgery were deemed relevant. Reference lists of key publications were also searched for relevant citations.

The National Guidelines Clearinghouse and individual guideline organizations were searched for practice guidelines relevant to this topic. A total of four clinical practice guidelines were identified from the following organizations: the National Cancer Institute, [20] the American Association of Ophthalmic Oncologists and Pathologists, [21] the Royal College of Ophthalmologists, [22] the Australian Cancer Network, [23] and the Université catholique de Louvain (Germany). [24]

TARGET POPULATION

The recommendations outlined in this guideline apply to patients with malignant uveal melanoma. Other ‘ocular’ melanomas arising in the conjunctiva, the eyelid, and the orbit are not included in this guideline.

RECOMMENDATIONS

Diagnosis and Work-Up

- Complete history.

- Complete ophthalmic examination and fundoscopy.

- Ocular ultrasonography (U/S) by a certified ophthalmic ultrasonographer or ophthalmologist with training in ultrasound.
    - 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.
    - B-scan U/S can allow for tumour measurement (height), and tumor characteristics including solidity/hollowness, vascularity, shape, and extra-scleral (extra-ocular) extension.
    - U/S biomicroscopy (UBM) is a high frequency ultrasound providing high resolution imaging of the anterior segment of the eye. It is used to visualize ciliary body and iris tumours.

- Ancillary ocular studies, if ophthalmic examination is inconclusive, sometimes due to media opacity.
    - Fluorescine 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.

- Staging work-up to rule out metastases of uveal melanoma.
    - Serum testing
        - CBC
        - Liver function tests
    - Diagnostic imaging
        - Option 1: CT of the chest and abdomen (liver protocol for abdomen)
        - Option 2: Whole body positron emission tomography (PET)-CT scan
        - If the patient is found to be high risk (i.e., gene expression profile class 2), baseline MRI of the liver is recommended.
        - If there is a suspicion of metastases, refer to the cancer centre.

Primary Management

Melanocytic Choroid Tumours

- Small (<3 mm in thickness) tumours (i.e., ‘nevi’, ‘indeterminate melanocytic lesions’, and small melanomas)
    - Small lesions are typically observed for growth or treated based on risk factors for growth and the associated risk of visual loss with treatment.
        - Most lesions are observed until growth is documented. Once growth is documented the lesion is labeled a melanoma and is treated.
        - Lesions are evaluated based on their risk factors for future growth.
            - Risk factors for future growth include: thickness>2mm, presence of subretinal fluid, visual symptoms, orange pigment, absence of drusen, margin near the optic nerve head, acoustic hollowness on ultrasound, and absence of a halo pigmentation pattern.
            - High risk lesions (3 or more risk factors) are often offered treatment, based on discussions with the patient regarding visual loss, since the risk of future growth is greater than 50%.
    - When indicated, treatment is most commonly ocular brachytherapy.

- Medium/intermediate (3-10 mm in thickness) tumours are typically treated with ocular brachytherapy.

- Large (>10 mm in thickness) tumours
  - Large lesions are typically treated with enucleation (eye removal) due to the risk of severe vision loss and neovascular glaucoma secondary to radiation complications.
  - Brachytherapy for large lesions is sometimes performed in select cases such as contralateral vision loss or in patients who insist on avoiding enucleation.

Ciliary Body Lesions

- Ciliary body lesions <10 mm thick and that do not have an extensive circumferential growth pattern are most commonly treated with brachytherapy.

- Ciliary body lesions are amenable to surgical excision (i.e., iridocyclecomy) in select cases.

Iris Lesions

- Iris lesions are typically observed for growth before brachytherapy treatment is offered.

- Iris lesions are amenable to surgical excision (i.e., iridectomy) in select cases.

- Iris lesions are often also amenable to brachytherapy.

Principles of Enucleation

- Enucleation involves surgical removal of the eye.

- Typically, lesions >10 mm in thickness and/or >18 mm in diameter are offered enucleation.

- For patients undergoing enucleation, in accordance with the College of American Pathologists' *Protocol for the Examination of Specimens from Patients with Uveal Melanoma*, [25] review of specimens should include reporting of the following elements:
  - Specimen size
  - Specimen laterality
  - Tumour site (macroscopic examination/transillumination)
  - Tumour basal size on transillumination (optional)
  - Tumour size after sectioning
  - Tumour location after sectioning (optional)
  - Tumour involvement of other ocular structures
  - Growth pattern
  - Histologic type
  - Histopathologic type
  - Histologic grade
  - Microscopic tumour extension
  - Margins
  - Pathologic staging (pTNM)
  - Additional pathologic findings (optional)
  - Comments (optional)

Principles of Primary Radiotherapy

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

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

Adjuvant Therapy

- If margins are positive or indeterminate after resection, adjunctive radiotherapy of the surgical margins is often utilized.

- 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 tumor abuts the optic nerve and overhangs the optic disc. Therefore TTT is not recommended as monotherapy for uveal melanoma.
    - TTT can be offered as an adjunctive treatment to reduce the risk of local recurrence following radiotherapy or as a primary treatment for medium risk nevi in select cases.
    - TTT is used in some centers to treat marginal recurrence post brachytherapy.
    - TTT can cause retinal vascular damage and retinal traction and their subsequent secondary visual loss.

Management of Patients with Metastatic Disease and High Risk Patients

- Currently there is no strong evidence to treat high risk patients (monosomy 3, GEP 2, or tumors >10 mm thick) without identified metastasis with adjuvant treatments to reduce the risk of developing identifiable metastasis. There is currently a great deal of interest on treating these patients and their 'micrometastatic' disease. Consideration for enrollment in clinical trials is warranted.

- Systemic therapy for the management of metastases:
    - Enrolment in a clinical trial is recommended.
    - There are no phase III data available on the use of systemic therapy for the management of metastatic uveal melanoma.
    - Phase II data have not demonstrated clinical efficacy in metastatic uveal melanoma with any of the tested single agents or combinations of agents.

- Surgical resection of solitary 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.

- Ablative techniques (i.e., thermoablation and radiofrequency ablation) have been used in the setting of metastatic uveal melanoma but require further study before their role is completely understood.

Follow-Up

Follow-up may consist of history and physical exam, chemistry, and imaging based on patient risk categories:

- Patients with gene expression profile class 1a or 1b, or disomy 3 (monosomy 3 negative or undetected) OR patients with no genetic assessment and tumour <8 mm thick:
    - Liver U/S: annually, indefinitely
    - Physical exam: annually, indefinitely
    - Follow-up may be transitioned to the family physician at 5 years.

- Patients with gene expression profile class 2, monosomy 3 (monosomy 3 positive or detected), OR tumours >8 mm thick with no genetic assessment:
    - Physical exam: annually, indefinitely
    - Annual liver U/S alternating with annual MRI liver for ten years, then yearly liver ultrasound indefinitely. If body habitus limits U/S, consideration for other modalities should be given.
    - Follow-up may be transitioned to the family physician at 10 years.

- Recently Multiplex-Ligation-Dependent probe amplification of chromosome 3 loss, 8q gain, and 6p gain has also become available commercially to assess for stratifying patients into low and high risk categories. Patients with loss of chromosome 3 and gain of 8q had the highest risk of metastasis (ten year 71% disease specific mortality), those with chromosome 3 loss and no gain in 8q where in the intermediate risk group (ten year 55% disease specific mortality), and those with no chromosome 3 loss were in the low risk group (ten year 0% disease specific mortality). [26]

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).

Recent research has demonstrated that earlier treatment, allowing for treatment of a smaller lesion, portends improved survival. [27] 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. [28] Therefore even melanocytic lesions ≤2 mm in thickness without any documentation of growth can be offered treatment. [28,29] The diagnosis of uveal melanoma can be very difficult for the non-specialist. [30,31] Treatment options for uveal melanocytic lesions involve both medical, laser, complicated extra-ocular and intra-ocular surgery, radiotherapy, radiosurgery, and other eye sparing treatment modalities. [32] Often observation versus treatment discussions, especially for small melanocytic lesions, require the balancing of treatments and their complications with the risk of observation and its threat to life; therefore published international guidelines, with Canadian representation, recommend patients be provided an evaluation/discussion with an eye cancer specialist (eye cancer specialist was defined as an ophthalmic oncologist, medical physicist, or radiation oncologist) [28] or ophthalmologist. [21,22] Similarly, 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. [33-36] For these reasons it is recommended that the provider be fully trained in all treatment areas (i.e., medical, complicated surgical,

radiotherapy, laser treatments of the eye, and cancer care) in order to safely follow, discuss, and treat all indeterminate (uveal melanocytic lesions that have not demonstrated growth) and malignant intra-ocular lesions.

Ocular U/S can be used to determine tumour size and shape, but orbital/ocular CT and MRI are not commonly used in diagnostic work-up, unless other examinations are inconclusive. [22,30] The common lesions on the differential diagnosis for uveal melanoma includes nevus, 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. [21] 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. [31]

Staging

Blood work typically consists of CBC and liver function tests (LFT). [22] Historically the most basic baseline imaging for ruling out systemic metastases consisted of CXR with abdominal U/S once LFT and physical examination was found to be too insensitive. However, these tests have since been shown to also have very low sensitivities (2% for LFT and 14% for liver ultrasound). [37] Therefore many centers utilize PET scanning or MRI abdomen and CT chest. Whole body PET-CT has demonstrated good sensitivity (41-100%) and positive predictive value (88-100%), [38,39] while the best sensitivity (67-92%) has been demonstrated with MRI. [39,40] The most current staging system adopted by most centers for uveal melanoma is the AJCC 7th edition. [8]

Two main issues need to be discussed. Some believe that little or no baseline imaging should be used in this population, based on the premise that metastases cannot be treated and the yield of finding metastasis at presentation is low. Yet it should be noted that the majority of patients (55%) have CT findings that require further investigation. [41] The treating surgeon should decide on the appropriate level of staging by also evaluating the second issue, based on balancing unnecessary testing with unnecessary surgery as many patients who demonstrate metastasis at presentation do not undergo treatment of their primary lesion.

Primary Management

Observation. Observation is only typically employed for indeterminate lesions. Yet, it is acceptable for very rare selected patients with uveal melanoma.[20] Observation is best suited for select cases of iris melanomas and small (1.0-3.0 mm in apical height and 5.0-16.0 mm largest basal diameter) choroidal melanomas. [19] The most common situation are low-grade melanomas (based on growth pattern) in patients with multiple other medical issues, including advanced age, that already carry a significant risk of mortality.

Indeterminate (typically small choroidal lesion or iris lesions) lesions are also often followed for documentation of growth. If risk factors for future growth are noted then treatment is often offered. Risk factors include: tumor thickness >2 mm, presence of subretinal fluid, visual symptoms, orange pigmentation, close proximity to the optic nerve head, absence of drusen, acoustic hollowness on ultrasound, and absence of a halo pigmentation pattern. [31,42-44] Lesions are often labeled as high risk nevi if they have 3 or more risk factors for growth. A retrospective analysis of data from patients with primary posterior uveal melanoma with documented tumor 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 ± SE 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 does not worsen survival. A different perspective using 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. [28]

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. [20] Enucleation involves surgical removal of the eye and has been the most widely used treatment, historically, until recently with new advances in radiotherapy. [20,45,46] Typically, lesions >10 mm in thickness and/or >18 mm in diameter are offered enucleation. Earlier concern over whether enucleation was promoting the release of tumour cells throughout the body, leading to observed increases in mortality post-enucleation, [46] contributed to the development of new management strategies, such as radiotherapy and transpupillary thermotherapy. Since then this Zimmerman hypothesis on seeding of tumor during enucleation has been disproved.[47]

Radiotherapy. For tumors whose location and dimensions allow for it, radiotherapy has largely taken the place of enucleation in the management of uveal melanoma. Radiotherapy options include episcleral brachytherapy, charged-particle external beam radiotherapy (EBRT) (i.e. protons, carbon ions, or helium ions), and photon-based radiosurgery (ie. linear accelerator, gammaknife, or cyberknife).

Isotopes most commonly used for episcleral plaque brachytherapy include Iodine-125, Palladium-103, and Ruthenium-106. [48] Treatment with ^{106}Ru should be limited to tumours with an apex height of less than 5 mm. Use of ^{125}I is consistent with the methods used in the collaborative ocular melanoma study (COMS), but ^{103}Pd may be considered for use as the two respective isotopes offer differences in intraocular dose distribution. Episcleral plaque brachytherapy using Iodine-125 is the treatment of choice for small to medium sized melanomas (<10 mm thick and <18 mm in largest basal dimension). High risk indeterminate lesions (i.e., those with three or more risk factors) are also typically offered treatment in select cases since the risk of future growth is greater than 50%. [28,43] Brachytherapy is preferred due to a large randomized controlled trial of 1337 patients that showed no difference in survival between brachytherapy and enucleation, [49] the potential for vision preservation by brachytherapy, 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 tumor, while ensuring the entire base of the tumor 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. [50,51] 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. [52]

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 prescribed in each case equivalent to 81.8 ± 2.2 Gy. [53]

The dose is delivered over 3-7 days, as per the recommendations of the American Brachytherapy Society. [54] 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. [48,50,51,55] 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. [48]

The COMS randomized trial of I-125 brachytherapy vs. enucleation as primary therapy, among patients diagnosed with choroidal melanoma (N=650) who were followed for 5 to 15 years, found no difference in survival outcomes and little difference in quality-of-life outcomes between groups. In fact, five-year survival was substantially better than expected based on published rates. [31,49,56,57] A retrospective case-series among patients diagnosed with uveal melanoma without metastases (N=400) and treated with palladium-103 brachytherapy (mean apical dose of 73.3 Gy over 5 to 7 continuous days) revealed a local control rate of 96.7%. Fourteen patients required secondary enucleation (5 for tumor growth and 9 for glaucoma pain control). The expected 5- and 10-year metastases-free survival rates were 92.7% and 86.6%, respectively.[58] Low recurrence rates were reported for iodine-125 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. [59] The COMS trial found that the risk of treatment failure (i.e., tumor growth, recurrence, or extrascleral extension) with I-125 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% CI, 10.0%-15.6%). Risk factors for treatment failure were older age, greater tumor thickness, and proximity of the tumour to the foveal avascular zone. Tumour control by radiotherapy is typically 95% (95% CI 93-96%) at 15 years. [60] 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. [61] Most cases of failed local control primarily treated with radiation are enucleated.

Charged-particle external beam radiotherapy (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 radiotherapy 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. [62] Similar results have been reported elsewhere. [63-67]

Transpupillary Thermotherapy. Transpupillary thermotherapy (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 adjunct to radiotherapy 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. [20] 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; 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. Closure of medium and large choroidal vessels was observed in 17 (35%) TTT patients and 44 (96%) brachytherapy patients (p<0.001). Choroidal vascular remodeling was detected in 20 patients (41%) in the TTT group vs. 16 patients (35%) in the brachytherapy group (p=0.693). [67]

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 radiotherapy. Local failure occurred in six patients (29%) and was associated with an increased number of TTT spots per session (p=0.023) and decreased tumor pigmentation (p=0.001). The radiotherapy plus TTT group regressed rapidly, with no local failures. No patient developed metastasis. TTT performed as a supplemental therapy in radiotherapy-resistant tumours (6 patients) or tumours at high risk for local failure with radiotherapy alone (3 patients) successfully induced tumour shrinkage and resolution of exudative retinal detachment in all 6 tumours radiotherapy-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. [68]

Management of Metastatic or Recurrent Disease. Local (ocular) recurrence is typically treated with enucleation or repeat brachytherapy. Some centers will utilize TTT for small recurrence at the margin of the tumor.

There is some data to suggest that resection of uveal melanoma metastasis in the liver may prolong survival. [69,70] A prospective study among twelve patients who underwent complete resection of metastasis demonstrated a median recurrence free survival (RFS) time of 19 months (6-78; 5-year RFS 15.6%) and an overall survival (OS) time of greater than 27 months (11-86; 5-year OS 53.3%). [71] Although without aggressive screening it is exceedingly uncommon to detect metastatic disease that is amenable to surgical resection. A study among 40 patients with hepatic melanoma metastasis (16 ocular and 24 cutaneous) who underwent resection demonstrated a median time to recurrence after hepatic resection of 8.3 months (ocular, 8.8 months versus cutaneous 4.7 months; p=0.30). Patients with primary ocular melanoma were more likely than patients with cutaneous melanoma to experience recurrence within the liver (53.3% vs. 17.4%; p=0.015). The 5-year survival rate for patients with a primary ocular melanoma was 20.5% (versus 0% for patients with cutaneous melanoma; p=0.03) and median overall survival was 29.4 months (versus 23.6 months for cutaneous mlenaoma; p=0.20). [72]

Systemic therapies for uveal melanoma have been largely modeled after therapies for cutaneous melanoma. There are no phase III data available on the use of systemic therapy for the management of metastatic uveal melanoma and, to date, phase II data have not demonstrated clinical efficacy in metastatic uveal melanoma with any of the tested single agents or combinations of agents. [73-89] Enrolment in a clinical trial is recommended. [20]

Chemotherapy. Systemic chemotherapy alone for the management of metastases or recurrent disease is largely ineffective. Over the past four years, clinical trials have tested the efficacy of carboplatin, paclitaxel, docosahexaenoic acid-paclitaxel, [68] and cisplatin by transarterial chemoembolization (TACE). [69] Of these, the most efficacious therapy was cisplatin TACE, with a partial response of 57%.[67] 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 domenstrated activity in patients with advance uveal melanoma in retrospective and expanded access studies. [90-95] Summarizing these six reports, 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 is slightly less than that reported in the phase III trials of the ipilimumab alone or combined with dacarbazine of 10.9% and 15.2% respectively.

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. Several targeted agents have demonstrated modest activity in patients with uveal melanoma, MEK inhibitors selumetinib and trametinib, and the c-KIT (CD117) inhibitor sunitinib. [74,96,97] Invariably resistance to these agents develops in a matter of months. These findings are early data on longer follow up are pending. Further study in larger scaled trials is warranted.

Local therapy in the setting of metastatic disease. 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 ($p<0.001$). [98] In general, surgery is a preferred option in younger patients with large tumours and in patients with a metastasis. [20] 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., thermoablation [99] and radiofrequency ablation [100]) have been used in the setting of metastatic uveal melanoma. 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. [101] As data on the use of this therapy are so limited, further study is needed before ablation can be recommended as a standard of care in the setting of uveal melanoma metastases.

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. [102] Some lower-level data are available on the usefulness of specific imaging tests and biochemical tests in the detection of metastasis. Since surgical resection and/or ablation evidence has suggested improved survival [101] most ocular oncology centers perform rigorous follow-up on high risk patients.

At baseline between 1.5 and 2% of patients with uveal melanoma will have liver metastasis identified with testing. [103-105] The median time to development of liver metastasis is approximately 2.5 years. [106] On CT evaluation for metastasis, 55% demonstrated hepatic abnormalities during baseline assessment. The management of metastatic disease may have more favorable outcomes when the metastasis is detected

early. [103] Therefore despite the low yield of detecting metastasis at baseline, baseline testing reduces most diagnostic dilemmas (including the need for liver biopsy) on follow-up imaging and their subsequent delays in possible treatment.

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, 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. [107]

Ultrasound has demonstrated very low sensitivity (i.e., 14%) for the detection of liver metastases. [37] The use of ultrasound in the follow-up of high-risk patients (i.e., those with gene expression profile class 2) should therefore complement other more sensitive tests. A study looking at the diagnostic value of combined positron emission tomography (PET)/CT scans in the follow-up of patients with metastatic uveal melanoma (N=12) reported that PET/CT scan showed vital metastases from uveal melanoma in 100% of patients. PET/CT scan also correctly identified a primary intraocular tumour, ruled out pulmonary involvement following suspicious CT scan and CXR in two patients, and confirmed an equivocal intrahepatic finding in an MRI scan as a vital metastasis. [38] These findings confirm earlier findings from an Australian study that looked at the sensitivity and specificity of (18)fluorodeoxyglucose (FDG)-PET compared to imaging or histopathology in uveal melanoma patients (N=22). FDG-PET showed sensitivity, specificity, and accuracy of 100%, 67% and 90%, respectively, a positive predictive value of 88% and a negative predictive value of 100%. [108]

Among the available imaging modalities, MRI of the abdomen, specifically of the liver, has a positive predictive value of 95% with a sensitivity of 67%, while PET has a positive predictive value of 100% but a sensitivity of only 45% (Table 3). [39] Thus, abdominal MRI may be of greater value than PET of the abdomen in the follow-up of patients with uveal melanoma. Damato et al. (2013) found that in a cohort of 188 high risk patients, MRI of the abdomen every 6/12 months detected metastasis before symptoms in 92% of patients. As a result 14% of patients with metastatic disease qualified for liver resection. All patients who underwent liver resection lived longer than one year following detection. Despite this study design not allowing for control of lead-time bias, it is clear that more lesions amenable to surgery were detected. [40] Prior research has suggested that surgical resection provides improved survival. [38]

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. [109-111] Nonetheless, there is sufficient evidence for sending patients diagnosed with uveal melanoma for a screening dermatologic examination to rule out cutaneous melanoma or other high risk lesions. 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 chest x-ray and liver ultrasound. [23,24] These assessments are typically performed annually, except in the case of patients with monosomy 3 or genetic expression profile class 2, who should undergo liver ultrasound every 3 months due to the increased risk of metastases.

Table 3. Accuracy of various imaging modalities in the detection of uveal melanoma metastases.

Author, Year	Modality	Metastases Site	Sensitivity	Specificity	Positive Predictive Value
Marshall, 2013 [109]	MRI	liver	92%	n/a	n/a
Orcurto, 2012 [112]	MRI PET-CT	liver	96% 35%	n/a	n/a
Freton, 2012 [111]	PET-CT (whole body)	any	n/a	94%	100%
Klingenstein, 2010 [107]	PET-CT (whole body)	liver or lung	100%	n/a	n/a
Servois, 2010 [39,38]	MRI PET	liver	67% 45%	n/a	95% 100%
Francken, 2006 [38]	PET	liver	100%	67%	88%
Finger, 2005 [113]	PET-CT (whole body)	any	100%	94%	100%
Semelka, 2001 [114]	MRI CT	liver	n/a	n/a	98% 75%
Eskelin, 1998 [115]	AST ALT AP LDH	liver	43% 38% 27% 67%	93% 90% 95% 96%	62% 68% 77% 35%
Hicks, 1998 [37]	CXR U/S AST AP	any	1.8% 14% 15% 25%	100% 100% 89% 86%	100% 100% 28% 33%

DISSEMINATION

- Present the guideline at the local and provincial tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services website.
- Send an electronic notification of the new guideline to all members of CancerControl Alberta.

MAINTENANCE

A formal review of the guideline will be conducted in 2016. If critical new evidence is brought forward before that time, the guideline working group members will revise and update the document accordingly.

GLOSSARY OF ABBREVIATIONS

Acronym	Description
CBC	complete blood count
CT	computed tomography
CXR	chest x-ray
EBRT	external beam radiotherapy
FDG	(18)fluorodeoxyglucose
MRI	magnetic resonance imaging
PET	positron emission tomography
TTT	transpupillary thermotherapy
U/S	ultrasound

CONFLICT OF INTEREST

Participation of members of the Alberta Cutaneous Tumour Team in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. There was no direct industry involvement in the development of this guideline. CancerControl Alberta recognizes that although industry support of research, education, and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some members of the Alberta Cutaneous Tumour Team are involved in industry-funded research or have other such potential conflicts of interest. However the guideline developers are satisfied it was developed in an unbiased manner.

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APPENDIX A

Uveal Melanoma Staging (modified from the American Joint Committee on Cancer Staging[8])

Table 4. Primary Tumour Definitions

	Iris	***Ciliary Body and Choroid***
Tx	Primary tumor cannot be assessed.	Primary tumor cannot be assessed.
T0	No evidence of primary tumor.	No evidence of primary tumor.
T1	Tumor limited to the iris.	Tumor size category 1.
T1a	Tumor limited to the iris; ≤ 3 clock hours in size.	Tumor size category 1 without ciliary body involvement and extraocular extension.
T1b	Tumor limited to the iris; > 3 clock hours in size.	Tumor size category 1 with ciliary body involvement.
T1c	Tumor limited to the iris with secondary glaucoma.	Tumor size category 1 without ciliary body involvement but with extraocular extension ≤5 mm in diameter.
T1d	-	Tumor size category 1 with ciliary body involvement and extraocular extension ≤5 mm in diameter.
T2	Tumor confluent with or extending into the ciliary body, choroid, or both.	Tumor size category 2.
T2a	Tumor confluent with or extending into the ciliary body, choroid, or both, with secondary glaucoma.	Tumor size category 2 without ciliary body involvement and extraocular extension.
T2b	-	Tumor size category 2 with ciliary body involvement.
T2c	-	Tumor size category 2 without ciliary body involvement but with extraocular extension ≤5 mm in diameter.
T2d	-	Tumor size category 2 with ciliary body involvement and extraocular extension ≤5 mm in diameter.
T3	Tumor confluent with or extending into the ciliary body, choroid, or both, with scleral extension.	Tumor size category 3.
T3a	Tumor confluent with or extending into the ciliary body, choroid, or both, with scleral extension and secondary glaucoma.	Tumor size category 3 without ciliary body involvement and extraocular extension.
T3b	-	Tumor size category 3 with ciliary body involvement.
T3c	-	Tumor size category 3 without ciliary body involvement but with extraocular extension ≤5 mm in diameter.
T3d	-	Tumor size category 3 with ciliary body involvement and extraocular extension ≤5 mm in diameter.
T4	Tumor with extrascleral extension.	Tumor size category 4.
T4a	Tumor with extrascleral extension ≤5 mm in diameter.	Tumor size category 4 without ciliary body involvement and extraocular extension.
T4b	Tumor with extrascleral extension >5 mm in diameter.	Tumor size category 4 with ciliary body involvement.
T4c	-	Tumor size category 4 without ciliary body involvement but with extraocular extension ≤5 mm in diameter.
T4d	-	Tumor size category 4 with ciliary body involvement and extraocular extension ≤5 mm in diameter.
T4e	-	Any tumor size category with extraocular extension >5 mm in diameter.

Table 5. Regional Nodes Definitions

NX	Regional lymph nodes cannot be assessed.
N0	No regional lymph node metastasis.
N1	Regional lymph node metastasis.

Table 6. Distant Metastases Definitions

M0	No distant metastases.
M1	Distant metastasis.
M1a	Largest diameter of the largest metastasis ≤3 cm.
M1b	Largest diameter of the largest metastasis 3.1–8.0 cm.
M1c	Largest diameter of the largest metastasis ≥8 cm.

Table 7. TNM Stage Definitions

	T	***N***	***M***
I	T1a	N0	M0
IIA	T1b-d	N0	M0
	T2a	N0	M0
IIB	T2b	N0	M0
	T3a	N0	M0
IIIA	T2c-d	N0	M0
	T3b-c	N0	M0
	T4a	N0	M0
IIIB	T3d	N0	M0
	T4b-c	N0	M0
IIIC	T4d-4	N0	M0
IV	Any T	N1	M0
	Any T	Any N	M1a-c

APPENDIX B

Evidence for systemic therapy in advanced uveal melanoma

Table 8. Clinical data on systemic therapy for advanced or metastatic disease.

Author (trial)	*Design*	*Treatments*	*Patients (n)*	*Response*	*Survival*	*Adverse events*
Bhatia S 2012 [73] (SWOG S0512)	phase II	carboplatin (AUC 6) + paclitaxel (225 mg/m^2) IV on day 1 plus sorafenib (400 mg) PO twice daily x 6	stage IV uveal melanoma w/ 0-1 prior systemic therapy (n=25)	overall: 0% (95% CI 0-14%)	PFS (med): 4 mos (95% CI 1-6 mos) PFS (6-mos): 29% (95% CI 13%-48%) OS (med): 11 mos (95% CI 7-14 mos)	
Mahipal A 2012 [74]	phase II	sunitinib malate (37.5 mg/d continuously) 4-week cycles 2nd line in 17/20 pts	metastatic uveal melanoma expressing c-kit (n=20)	partial: 1 patient stable disease: 12 patients	OS (med): 8.2 mos PFS (med): 4.2 mos	fatigue: 90% diarrhea: 60% hemorrhage: 55% anorexia: 45% hand-foot syndrome: 25% hypothyroidism: 25% rash: 25%
Homsi J 2010 [75]	phase II	docosahexaenoic acid (DHA)-paclitaxel (500 mg/m²/week) IV for 5 weeks (6-week cycles)	metastatic uveal melanoma chemo-naive or previously treated (n=22)	stable disease: 32%	OS (med): 9.8 mos	neutropenia: 23% musculoskeletal pain: 10%
Huppert PE 2010 [76]	phase II	cisplatin (100mg/m^2) by transarterial chemo-embolization (TACE) carboplatin in 3/14 pts due to kidney function	metastatic uveal melanoma; liver mets (n=14)	partial: 8 patients (57%) stable disease: 4 patients (29%) progression: 2 patients (14%) (med time to progression: 8.5 mos)	OS (med): 11.5 mos (3-69) *subgroup analysis (mets <25% vs. ≥25%):* 17 vs. 11 mos (p=0.18)	
Fiorentini G 2009 [77]	phase II	transarterial chemo-embolization (TACE) beads preloaded with irinotecan (100 mg)	metastatic uveal melanoma; liver mets (n=10)	objective response: 100% partial response: 10	med f/u 6.5 mos OS: 80% (8/10 alive at the time of analysis)	abdominal pain
van Iersel LB 2008 [116]	phase II	hyperthermic IHP with melphalan (200 mg)	melanoma with liver mets (n=18; 12 had uveal melanomas)	uveal melanoma patients: partial response: 4 pts stable disease: 6 pts progressive: 2 pts	DFS (med): 6.6 mos OS (med): 10.0 mos	no treatment-related mortality grade 3-4 hepatoxicity: 10 pts (56%) veno-occlusive disease: 4 pts

Author (trial)	*Design*	*Treatments*	*Patients (n)*	*Response*	*Survival*	*Adverse events*
O'Neill PA 2006 [78]	phase II	dacarbazine (850 mg/m^2) plus treosulfan (8 g/m^2) q 3 weeks for a max of 6 cycles (1st line)	metastatic uveal melanoma (n=15)	overall: none stable disease: 2 patients	DFS (med): 12 weeks OS (med): 30 weeks	major toxicities were haematological (particularly thrombocytopaenia)
Schmittel A 2006 [80,82]	phase II	1. gemcitabine (1000 mg/m^2) + treosulfan 2. treosulfan alone (3500 mg/m^2)	metastatic uveal melanoma chemo-naive (n=48)	stable disease: 7 patients in the gem-T group vs. 3 patients in the treosulfan group (p=.08) partial: 1 patient in the gem-T group vs. none in the treosulfan group	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) 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	grade 3-4: leukopenia: 4 gem-T vs. 0 T nausea: 3 gem-T vs. 3 T FN: 2 gem-T vs. 0 T
Patel K 2005 [81]	phase II	1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) dissolved in ethiodized oil for hepatic artery chemoembolization	metastatic uveal melanoma; mets to liver (n=24)	complete response: 1 patient partial response: 4 patients stable disease: 13 patients	OS (med): 5.2 mos (0.1-27.6 months) *OS (med) by subgroup:* pts w/ CR/PR = 21.9 mos (7.4-27.6 mos) pts with stable disease: 8.7 mos (2.9-14.4 mos) pts with progressive disease: 3.3 mos (1.6-5.6)	
Schmidt-Hieber M 2004 [79]	phase II	bendamustine (120 mg/m^2 days 1 and 2) q 3 weeks	metastatic uveal melanoma; progression during or after 1st line chemo (n=11)	progressive disease: all 11 pts	n/a	grade 3-4: anemia (2 pts), thrombocytopenia (1 pt), leukocytopenia (2 pts)
Agarwala SS 2004 [83]	phase II	cisplatin (100 mg/m^2 starting; increased in 25% increments to a max 125 mg/m^2)	metastatic uveal melanoma; liver mets (n=19)	overall response rate: 16%	n/a	any: renal, hepatic and haematological
Alexander HR Jr 2003 [83,84]	phase II	hyperthermic IHP with melphalan (1.5 mg/kg; mean total 105 mg)	metastatic ocular melanoma; liver mets (n=29)	complete response: 3 pts (10%), lasting 12-15 mos partial response: 15 pts (52%), lasting 10 mos (mean)	med f/u: 30.7 mos PFS (med): 8.0 mos OS (med): 12.1 mos	NR
Kivelä T 2003 [86]	phase II	bleomycin, vincristine, lomustine, dacarbazine q4 w x 2 cycles + IFN alpha-2b (3 x 10^6 IU)	metastatic uveal melanoma (n=24)	objective response: 0% stable disease: 2 pts (8.3%) progression: 20 pts	PFS (med): 1.9 mos (95% CI: 1.8-3.4 mos) OS (med): 10.6 mos (95% CI: 6.9-16.4 mos)	grade 3: alopecia and neurotoxicity in 13% of pts

Author (trial)	*Design*	*Treatments*	*Patients (n)*	*Response*	*Survival*	*Adverse events*
Bedikian AY 2003 [87]	phase II	temozolomide (75 mg/m^2 per day orally for 21 days) q 4 weeks	metastatic choroidal melanoma (n=14)	complete response: none partial response: none stable disease: 2 pts	n/a	n/a
Pyrhönen S 2002 [88]	phase II	bleomycin, vincristine, dacarbazine, lomustine q 4 weeks plus IFN (3 x 10^6 IU)	metastatic uveal melanoma; liver mets (stage IVB; n=20)	partial response: 3 (15%; 95% CI 0-38) stable disease: 11 (55%; 95% CI 32-77) after 2+ cycles	stage IVBa: 17 mos (95% CI 4-37) stage IVBb: 11 mos (95% CI 1-23)	grade 3-4 hematologic toxicity, either leukopenia or thrombocytopenia
Becker JC 2002 [89]	phase II	fotemustine (100 mg/m^2) into the hepatic artery or peripheral vein	metastatic ocular melanoma (n=48)	objective response: 21.7% for intra-arterial vs. 8% for peripheral vein	OS (med): 369 days for intra-arterial vs. 349 days for peripheral vein	n/a