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PRACTICE GUIDELINE

Management of uveal melanoma: a consensus-based provincial clinical practice guideline

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ABSTRACT

Introduction Survival in uveal melanoma has remained unchanged since the early 1970s. Because outcomes are highly related to the size of the tumour, timely and accurate diagnosis can increase the chance for cure.

Methods A consensus-based guideline was developed to inform practitioners. PubMed was searched for publications related to this topic. Reference lists of key publications were hand-searched. The National Guidelines Clearinghouse and individual guideline organizations were searched for relevant guidelines. Consensus discussions by a group of content experts from medical, radiation, and surgical oncology were used to formulate the recommendations.

Results Eighty-four publications, including five existing guidelines, formed the evidence base.

Summary Key recommendations highlight that, for uveal melanoma and its indeterminate melanocytic lesions in the uveal tract, management is complex and requires experienced specialists with training in ophthalmologic oncology. Staging examinations include serum and radiologic investigations. Large lesions are still most often treated with enucleation, and yet radiotherapy is the most common treatment for tumours that qualify. Adjuvant therapy has yet to demonstrate efficacy in reducing the risk of metastasis, and no systemic therapy clearly improves outcomes in metastatic disease. Where available, enrolment in clinical trials is encouraged for patients with metastatic disease. Highly selected patients might benefit from surgical resection of liver metastases.

Key Words Uveal melanoma, ocular melanoma, choroidal melanoma, ciliary body melanoma, iris melanoma, melanoma, ophthalmology, practice guidelines

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INTRODUCTION

Melanoma of the uveal tract (that is, iris, ciliary body, and choroid), sometimes called "ocular melanoma," accounts for 5% of all melanomas and occurs at a rate of about 6 cases per million person–years[1,2]. Nevertheless, melanoma is the most common primary intraocular malignancy, and after the skin, the uveal tract is the 2nd most common location for melanoma[2]. Risk factors include white race, light eye color, fair skin, cutaneous and iris nevi and freckles, and an inability to tan[3–6]. Despite advances in our understanding of the disease, the overall survival (OS) rate has not improved since the early 1970s[7]. The disease-specific mortality rate at 15 years is 45%[8], and no successful treatments for metastatic uveal melanoma have been developed to date[9].

Factors associated with poor prognosis include large tumour size, tumour location in the ciliary body, intermediate or epithelioid cell type, proximity to the location of the tumour anterior margin, presence of extraocular extension, high mitotic rate, and lymphocytic infiltration[10–12]. Two genetic tests more precisely identify patients with worse prognosis: testing for monosomy 3 and gene-expression profiling (GEP). Monosomy 3, with a gain in chromosome 8q, and GEP class 2 are associated with 3-year metastasis-free survival rates of 53% and 50% respectively[8,13,14]; these genetic variations occur in about 50% of patients[13,15–18]. A prospective validation study of GEP class 2 showed that, on multivariate analysis, GEP class was the only significant factor[14]. Subsequent work has demonstrated that tumour size (basal dimension) is

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an independent predictor of survival for GEP class 1 and 2 patients alike[19].

The management of uveal melanoma is complex and often requires a multidisciplinary team of specialists. No published Canadian guidelines are available to suggest appropriate strategies for the diagnosis, treatment, and follow-up of patients with uveal melanoma. We therefore aimed to develop a consensus-based, evidence-informed guideline for the management of uveal melanoma. The intended readership includes ophthalmologists, oncologists, and family physicians involved in the follow-up care of patients with this disease. For the purposes of the present guideline, other non-uveal ocular melanomas arising in the conjunctiva, the eyelid, and the orbit are not included.

The aim for the guideline was that it address these 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?

METHODS

The literature review process for the guideline was developed based on published guidance from the U.K. National Institute for Health and Clinical Excellence[20], the *Archives of Pediatrics and Adolescent Medicine*[21], and the AGREE Collaboration[22]. With that methodologic foundation, the guideline recommendations were drafted by an ophthalmologist dually appointed to the University of Alberta (Edmonton, AB) and the University of Calgary (Calgary, AB) and by a cancer research methodologist. The guideline was then reviewed by an expert panel of surgical oncologists, radiation oncologists, medical oncologists, and dermatologists and was endorsed by the Alberta Cutaneous Tumour Team.

The evidence base for the guideline was informed by a systematic review of the literature. Using the terms "uveal melanoma," "ocular melanoma," and "intraocular melanoma," PubMed was searched (2000 through December 2014) for English-language publications including clinical trials, meta-analyses, and guidelines. Small studies (that is, fewer than 10 patients) and those that did not report outcomes related to the efficacy of treatments or imaging modalities for uveal melanoma were excluded. Reference lists of key publications were also searched for relevant citations. The U.S. National Guidelines Clearinghouse and the Web sites of individual guideline organizations were searched for clinical practice guidelines relevant to the topic. Throughout the review process, authors were allowed to add new publications to the evidence base if they met the original inclusion criteria.

RESULTS

Eighty-four publications formed the basis for the recommendations. Literature was identified for diagnosis and staging, observation, surgery, brachytherapy, transpupillary thermotherapy (TTT), management of metastatic disease, and follow-up. Among the relevant publications were five guidelines from the U.S. National Cancer Institute[23], the American Association of Ophthalmic Oncologists and Pathologists[24], the Royal College of Ophthalmologists (United Kingdom)[25], the Australian Cancer Network[26], and the Université catholique de Louvain[27]. No Canadian guidelines were identified.

DISCUSSION

Diagnosis and Referral

The timely management of uveal melanocytic lesions, including small flat lesions, is vitally important, because any delay in referral of an early melanoma could result in significant growth and subsequent loss of vision, loss of the eye (that is, enucleation), and loss of life because of metastasis. Waiting for observation of growth, even in small melanocytic lesions (≤2 mm thickness) identified as clinically suspicious by an ophthalmologist, can increase the risk of metastasis[28,29]; such lesions can therefore be offered treatment[30].

Because uveal melanoma and indeterminate lesions are complex eye conditions, with diagnoses that are often very difficult for the non-specialist[30,31] and because treatment options require the balancing of benefits against complications (that is, risk of observation compared with treatment), international guidelines recommend that patients be provided an evaluation by an eye cancer specialist (that is, ophthalmic oncologist, medical physicist, or radiation oncologist)[30] or an ophthalmologist[24,25]. The provider should be trained in all treatment areas (that is, medical, surgical, radiotherapy, laser therapy, and cancer care) so as to safely follow, discuss, and treat all indeterminate lesions and malignant intraocular lesions.

Ocular ultrasonography (US) can be used to determine tumour size and shape. Orbital or ocular computed tomography (CT) and magnetic resonance imaging (MRI) are not commonly used during diagnostic work-up unless other examinations are inconclusive[25,31]. The differential diagnosis for uveal melanoma includes ephelis, 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[24]. Experienced ophthalmologists with a practice focus in oncology are able to diagnose uveal melanoma based predominantly on funduscopy and US (that is, without biopsy) with 98% accuracy[32].

Recommendations: The evaluation and treatment of uveal melanoma and indeterminate intraocular lesions is complex. Observation with subsequent delay in therapy, even in small intraocular malignancies (≤2 mm thickness), can increase in the risk of metastasis. Therefore, all intraocular malignancies and indeterminate lesions should be evaluated by a provider trained in all aspects of care (that is, medical, oncologic, surgical, radiotherapy, laser therapy) to determine appropriate treatment.

Staging

Staging is guided by the American Joint Committee on Cancer system for uveal melanoma[10]. Staging requires intraocular examination, serum tests, and imaging. Blood

work typically consists of complete blood count and liver function tests[25]. Historically, the most basic baseline imaging for ruling out systemic metastases consisted of plain chest radiography, with abdominal US. However, those tests have since been shown to have low sensitivity[33] and have largely been replaced by combined positron-emission tomography (PET)–CT imaging, abdominal MRI and chest CT imaging, or CT imaging of chest and abdomen. Whole-body PET-CT imaging has demonstrated good sensitivity (35%–100%) and positive predictive value (88%–100%)[34–36], and MRI has shown the highest sensitivity (67%–92%)[36,37].

Controversy surrounds the question whether baseline imaging should be performed in the affected population, because of the premise that metastases cannot be treated and the fact that the yield of positive findings at presentation is low. It should be noted, however, that more than half the affected patients (55%) have abdominal CT findings that require further investigation[38], with most being false positives; only 2% of patients have definitive metastasis at staging[38]. It might therefore be best to clarify the baseline imaging findings early, so as 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 are often spared aggressive treatment of their primary lesion.

Recommendations: Staging work-up to rule out metastases of uveal melanoma should include serum testing (complete blood count and liver function tests) and diagnostic imaging using one of these schema:

- CT of chest and abdomen (liver protocol for abdomen)
- Whole body PET-CT imaging
- Liver MRI and chest CT

If metastasis is suspected, the patient should be referred to a cancer centre.

Primary Management

Observation

Observation is typically reserved for indeterminate lesions, but can be acceptable for rare selected patients with melanoma of the iris and small choroidal melanomas (that is, <3.0 mm apical height and <10.0 mm basal diameter)[24]. Most patients selected for observation present with a low-grade tumour, have multiple comorbidities, or are at an advanced age and already carry a limited expected survival[24].

Risk factors for future growth of indeterminate lesions include tumour thickness greater than 2 mm, subretinal fluid, visual symptoms, orange pigmentation, close proximity to the optic nerve head, absence of drusen, acoustic hollowness on US, and absence of a halo pigmentation pattern[39–41]. If the foregoing risk factors are present, treatment should be considered. Waiting for documented growth of lesions can increase the risk of metastasis by a factor of up to 8[28], and improved survival has been demonstrated with earlier management[29].

The 7th edition of the American Joint Committee on Cancer classification system has demonstrated that tumour size predicts survival[42]. Furthermore, more recent work has found that, even after controlling for GEP, tumour size (that is, basal dimension ≥ 12 mm) is an independent predictor of metastasis at 5 years[19]. In contrast, several small non-comparative case series have suggested that patients with small indeterminate lesions who are carefully selected by an ophthalmologist can be observed for tumour growth before treatment initiation without adversely affecting survival[43–47]. The American Brachytherapy Society guidelines suggest that patients being observed should be counselled about the small (yet still unquantified) increased risk of metastasis with observation[30].

Recommendations: Observation is not recommended for uveal melanomas except in unique situations. Indeterminate lesions should undergo a complete ophthalmologic assessment of risk factors for future growth. The presence of risk factors necessitates discussion for treatment, including future risk of growth and metastasis balanced with the risk of visual loss from treatment.

Surgery

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; historically, it was the most widely used treatment until recent advances in radiotherapy[24,47]. Patients with lesions exceeding 10 mm in thickness or 18 mm in diameter (or both) are still offered enucleation as the preferred treatment because of the complications connected to delivering high-dose radiation to the eye. Concerns about enucleation potentially promoting the hematogenous release of tumour cells and possibly leading to increased mortality after enucleation[48] have contributed to the development of new management strategies such as radiotherapy and TTT. Subsequently, however, the Zimmerman hypothesis concerning the seeding of tumour during enucleation has been disproved[49].

Recommendations: Enucleation is most often reserved for lesions more than 10 mm in thickness or 18 mm in diameter (or both) because of complications secondary to radiation, including the risk of severe vision loss and loss of the eye. Selected ciliary body lesions and iris lesions might be amenable to excision (that is, iridocyclectomy and iridectomy respectively).

Brachytherapy

Radiotherapy has largely replaced enucleation for tumours of suitable location and dimension (that is, less than 10 mm in thickness and 18 mm in largest basal diameter). Larger tumours carry a risk of vision loss and radiation complications because of neovascular glaucoma; however, radiotherapy is sometimes used in patients with large tumours and a strong preference for attempting eye-sparing treatments. Radiotherapy options include episcleral brachytherapy, charged-particle external-beam radiotherapy (that is, protons, carbon ions, or helium ions), and photon-based radiosurgery [that is, linear accelerator,

Gamma Knife (Elekta, Stockholm, Sweden), or CyberKnife (Accuray, Sunnyvale, CA, U.S.A.)].

Brachytherapy has become the treatment of choice based on the results of the Collaborative Ocular Melanoma Study (COMS), a randomized controlled trial in 1317 patients that showed equivalent survival for brachytherapy and enucleation[50–52]. Brachytherapy provides accurate and continuous administration of radiation and has the added benefit of vision preservation and improved cosmesis[53]. The most commonly used isotopes include ^{125}I, ^{103}Pd, and ^{106}Ru[54–56]. The choice of isotope is often based on tumour depth. High-risk indeterminate lesions that carry a greater than 50% risk of growth could be offered brachytherapy in selected cases[28,40,57].

The COMS trial found that the risk of treatment failure (that is, tumour growth, recurrence, or extrascleral extension) with ^{125}I was low (10.3%; 95% confidence interval: 8.0% to 13.2%). Predictors of failure included older age, greater tumour thickness, and proximity of the tumour to the foveal avascular zone[54]. The reported local control rate with ^{103}Pd is also quite high (96.7%), with only 14 of 400 patients requiring secondary enucleation[55]. A retrospective analysis of patients with uveal melanomas 16 mm or less in basal diameter and large height by the COMS criteria also reported a low recurrence rate with ^{125}I (7%)[58]. Local failure after radiation for posterior uveal melanoma should be re-treated with either enucleation or brachytherapy[59]. In some centres, minimal margin recurrence can also be treated with TTT[60].

Recommendations: Lesions best suited for brachytherapy include high-risk indeterminate lesions and lesions less than 10 mm in thickness and 18 mm in maximum diameter; larger tumours can be offered brachytherapy in selected cases. Selected ciliary body lesions less than 10 mm thick without an extensive circumferential growth pattern and selected iris lesions can also be considered for brachytherapy.

Transpupillary Thermotherapy

Transpupillary thermotherapy uses an infrared laser through a dilated pupil. Because of high recurrence rates, TTT is generally not used as a primary treatment for uveal melanoma; rather, it is used as an adjunct to radiotherapy or to treat medium-risk nevi or indeterminate lesions. Because of penetrance limitations, TTT is best suited for small lesions (<3.0 mm in apical height and <16.0 mm in largest basal diameter)[23]. The recurrence rate for primary treatment of small melanomas with TTT is as high as 29%, significantly higher than the rates seen with plaque brachytherapy[61,62]. The role for TTT as an adjunct to radiotherapy is based on data from a retrospective case-matched comparative study ($n = 36$) and a retrospective observational study ($n = 21$) that were conducted in parallel to compare TTT alone with TTT plus plaque radiotherapy. The data showed that the local failure rate with TTT alone was 29% (that is, 6 patients); in the radiotherapy plus TTT group, regression was rapid, with no local failures, and no patient experienced metastasis[63]. Transpupillary thermotherapy can also be used to treat marginal recurrence after brachytherapy[60]; a complete response rate of 29% has been reported[64].

Recommendations: Because of a relatively high rate of local recurrence, TTT is not recommended as a primary therapy for uveal melanoma. In choroidal melanoma, to reduce the risk of local recurrence after radiotherapy or as a primary treatment for medium-risk nevi, TTT can be offered as an adjunct treatment in select cases.

Medical Management in the Setting of High-Risk or Metastatic Disease

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). Furthermore, most systemic therapies for metastatic uveal melanoma (largely modelled after therapies for cutaneous melanoma) have failed to demonstrate clinical efficacy in phase II trials[65–81]. However, immunotherapies, including the anti-CTLA4 antibody ipilimumab, have shown some success in retrospective and expanded-access studies[82–87]. Pooling those publications, 188 patients with advanced uveal melanoma treated with ipilimumab experienced 1 complete response, 7 partial responses, and 52 incidences of stable disease. The resulting response rate was 4.3%, with a disease control rate of 31.9%. That response rate is slightly less than the rates reported in phase III trials of ipilimumab alone or combined with dacarbazine for cutaneous melanoma (10.9% and 15.2% respectively). More 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 MEK pathway. Several targeted agents, including the MEK inhibitors selumetinib and trametinib, and the C-kit (CD117) inhibitor sunitinib, have demonstrated modest activity in patients with uveal melanoma[88,89]. Invariably, resistance to those agents develops within months of therapy initiation. Further study in larger trials is warranted.

Recommendations: There is no evidence to support the use of adjuvant systemic therapy in high-risk patients (monosomy 3, GEP class 2, or tumours > 10 mm thick). Evidence to support the use of systemic chemotherapy for the management of metastatic uveal melanoma is lacking. Immunotherapy with ipilimumab and targeted therapy with MEK inhibition appear promising, but to date have generally been palliative. Patients should be considered for enrolment in clinical trials.

Surgical Resection in the Setting of Metastatic Disease

Some data suggest that resection of liver metastases from uveal melanoma might prolong survival[90,91], including data from a single-arm prospective study in 12 patients who were able to achieve a median recurrence-free survival of 19 months (range: 6–78 months; 5-year recurrence-free survival: 15.6%) and an OS of 27 months (range: 11–86 months; 5-year OS: 53.3%) after complete resection[92]. Retrospective data also suggest that, compared with no surgery, resection of liver metastases is associated with a median survival that is increased by a factor of 3.7[93]. Similar data have been reported elsewhere[94–96]. However, the results in those noncomparative cohorts could be influenced by lead-time bias or favourable tumour biology in patients who are candidates for resection. Nevertheless, without intensive

screening, detection of metastatic disease that is amenable to surgical resection is uncommon. Surgery to remove metastases is usually reserved for younger patients[24].

Surgical resection in combination with chemotherapy might offer some benefit to patients with metastatic disease. A prospective study of aggressive hepatic surgery and implantation of an intra-arterial catheter for the delivery of chemotherapy (for example, fotemustine or dacarbazine–platinum, or both, for 4–9 cycles) in 75 patients with liver metastases demonstrated complete responses in 27.5% and significant tumour reductions in 49.3%. Median OS was 10 months in patients who received complete surgery plus chemotherapy[97]. Similar findings have been reported elsewhere[98]. Further study incorporating new agents, especially immunotherapeutic agents, will be of interest, and clinical trial participation is encouraged. Until longer OS is achieved, intrahepatic treatment should be considered experimental.

Recommendations: Highly selected patients should be considered for surgical resection of potentially resectable liver metastasis. Most patients with metastatic disease will present with diffuse involvement of the liver and therefore will not qualify for surgical resection.

Ablation in the Setting of Metastatic Disease

Ablative techniques—that is, thermoablation[99] and radiofrequency ablation (RFA)[100]—have been used in the setting of metastatic uveal melanoma. Data from a retrospective study in 8 patients with liver metastasis from ocular melanoma revealed a success rate of 50% with surgery or RFA, or both. In that series, 1 patient underwent left lateral segmentectomy, and 3 received combinations of left lateral segmentectomy, wedge resection, and RFA of 2–4 lesions. Median survival was 46 months in patients who underwent surgery alone or in conjunction with RFA to address all liver lesions[101].

Recommendation: The data are insufficient to provide guidance on the role of ablative techniques in the setting of uveal melanoma metastatic to liver. Further study is required.

Follow-Up

No high-level studies are available to inform the most appropriate monitoring for patients who have undergone treatment for uveal melanoma. As such, no consensus has been reached within the ophthalmic or oncologic community about the role of surveillance for detection of metastases in those patients. Because evidence concerning surgical resection has suggested improved survival[102], there is a trend toward the use of rigorous follow-up in high-risk patients. The median time to develop liver metastases is approximately 2.5 years; management of metastatic disease might therefore achieve more favourable outcomes when the metastasis is detected early[102].

Clinical characteristics and tumour genetics predict survival. A customized follow-up routine based on the patient's risk category is therefore recommended. Ultrasonography has demonstrated high specificity (100%), but low sensitivity (14%) for the detection of uveal melanoma liver metastases[33]. The use of US 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[34,103–107]. Magnetic resonance imaging offers consistently good sensitivity (92%–96%); the sensitivity 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%, $p = 0.01$), and positive predictive value was slightly higher with PET-CT (95% vs. 100%, $p = 0.01$)[35]. 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 qualifying for liver resection[104]. Consensus-based guidelines recommend that follow-up consist of annual history and physical exam, liver function tests, PET-CT or MRI of abdomen, plain radiography of chest, and liver US[25–27]. High-risk patients require more frequent imaging. To date, no data on the impact of follow-up on survival are available.

Recommendations: Low-risk patients (that is, GEP class 1a or 1b; no monosomy 3 detected; or tumour <9 mm thick and no genetic assessment) should receive annual liver US and a physical exam, indefinitely; follow-up can be transitioned to the family physician at 5 years. High-risk patients (that is, GEP class 2; monosomy 3 detected; or tumour ≥9 mm thick and no genetic assessment) should receive an annual physical exam, indefinitely, plus imaging every 6 months, consisting of liver US alternating with abdominal or liver MRI, for 10 years. If the body habitus limits US, other modalities should be considered. Follow-up can be transitioned to the family physician at 5–10 years.

CONCLUSIONS

The management of uveal melanoma and indeterminate intraocular lesions is complex and requires multidisciplinary input by experienced specialists with training in ophthalmologic oncology. With appropriate care, many patients can recover from their malignancy. However, more work is needed to understand the role of systemic therapy in the prevention and management of metastatic disease. Enrolment of patients into clinical trials should be encouraged whenever trials are available.

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CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

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