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ORIGINAL RESEARCH

Uveal Melanoma: A Review of the Literature

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ABSTRACT

Melanomas affecting different components of the uvea occur with differing frequencies and clinical presentations. Uveal melanoma is diagnosed via funduscopic exam and ancillary tests. These lesions may present with visual findings or incidental findings on physical exam. Metastasis occurs in approximately half of all patients with primary uveal melanoma. The liver is the most common site of metastasis. Enucleation was at one time considered the definitive local treatment for primary uveal melanoma, but has been largely replaced by other therapeutic procedures that aim to prevent metastasis while preserving vision. Unfortunately, metastasis of uveal melanoma almost always proves to be fatal. The current treatment of metastatic uveal melanoma is limited by the intrinsic resistance of uveal melanoma to conventional systemic therapies. Advancements in molecular biology have resulted in the identification of a number of promising prognostic and therapeutic targets. Early detection and therapy are important factors in disease survival. It is imperative that the treating physician be familiar with the clinical features of uveal melanoma and distinguish it from mimickers in order to ensure effective and timely treatment.

Keywords: Choroid; Ciliary body; Iris; Melanoma; Review

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INTRODUCTION

Uveal melanoma is the most common primary cancer of the eye in adults [1]. Although both uveal and cutaneous melanomas both originate from melanocytes, their underlying pathogenesis and clinical behavior differ significantly [2].

In the past decade, many details surrounding the underlying pathogenesis of uveal melanoma have emerged, revealing a complex and evolving story. Cytogenetic and molecular genetic features of the uveal cells have been demonstrated to have strong prognostication value in uveal melanoma [3].

The natural history of uveal melanoma often involves the development of metastasis, an event associated with poor prognosis [4].

Therefore, it is imperative that the treating physician be familiar with the clinical features of uveal melanoma allowing for early treatment and aversion of potentially life-threatening metastasis [5].

Uveal melanoma restricted to a limited anatomical region may be controlled by local and locoregional treatments. However, the treatment of metastatic uveal melanoma is limited by the lack of effective systemic treatments [1]. This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

EPIDEMIOLOGY

Uveal melanoma originates from melanocytes residing in the uveal tract [1]. Approximately 90% of uveal melanomas arise in the choroid, 7% in the ciliary body, and the remaining 3% in the iris [6]. Yet, uveal melanoma is a relatively rare condition. A study based on the National Cancer Database of the USA examined cases of cutaneous and non-cutaneous melanomas between 1985 and 1994. Ocular melanomas constituted 5.2% of identified cases, of which uveal melanoma comprised 85% [7]. Similar results have been reported in other countries with predominantly White populations [8–11].

Numerous epidemiological studies have examined factors that may increase the risk of uveal melanoma. The risk factors that have been identified and extensively studied include age, gender, race and ethnicity, choroidal nevi, and ocular/oculodermal melanocytosis [2]. The average age of initial diagnosis of uveal melanoma is approximately 60 years [7, 12]. Compared with older patients, younger patients are more likely to present with iris melanomas, have associated melanocytosis, and a lower risk of metastatic disease [13]. Pediatric and congenital cases have been reported, but seldom occur [2, 14]. Although it is uncertain whether or not gender-specific differences in uveal melanoma incidence exist, most symptomatic patients are men [2, 15]. With respect to race and gender, uveal melanoma predominantly affects Caucasians. An analysis of the SEER database from 1992 to 2000 reported that the annual age-adjusted incidence per million for uveal melanoma was 0.31 in Blacks, 0.38 in Asian and Pacific Islanders, 1.67 in Hispanics, and 6.02 in non-Hispanic Whites [16]. Intrinsic host factors that predispose Caucasians to uveal melanoma include ancestry from northern latitudes, fair skin color, light eye color, and propensity to sunburn [17, 18].

Up to half of patients with uveal melanoma will develop distant metastasis, with metastatic spread occurring hematogenously [1]. The Collaborative Ocular Melanoma Study (COMS) identified the 5- and 10-year cumulative metastasis rates of 25% and 34%, respectively [19]. The liver is the most common site of metastasis and is involved in 90% of individuals who develop metastatic disease. The median survival of uveal melanoma patients with liver involvement is reported to be 4–5 months, with a 1-year survival of 10–15% [20, 21]. About 50% of these patients with liver metastasis have extrahepatic involvement. The most common extrahepatic metastasis sites are the lungs (30%), bone (23%), and skin (17%) [22].

The most important predictive factors for metastatic disease include basal tumor diameter, the involvement of the ciliary body, extrascleral extension, epithelioid melanoma cytology, microvascular density, high mitotic rate, chromosome 3 loss, chromosome 1p loss, chromosome 6p gain, and chromosome 8q gain [23–26].

PATHOGENESIS

Alterations on the genetic, molecular, and macroscopic level appear to be instrumental in the development and continued evolution of uveal melanoma. There is evidence that alterations in the function and expression of tumor suppressor pathways allow melanocytes in the uveal tract to enter the cell cycle and undergo unregulated proliferation. The earliest disruptions appear to occur in the retinoblastoma (Rb) tumor suppressor pathway. The Rb protein inhibits the progression of the cell cycle at the G1-S phase checkpoint. In uveal melanoma, Rb is inactivated by hyperphosphorylation [3, 27].

In two-thirds of uveal melanomas this occurs directly via cyclin D overexpression, in the other one-third this process is mediated indirectly by methylation and inactivation of the *INK4A* gene. *INK4A* encodes a tumor suppressor protein (p16Ink4a) that activates Rb by inhibiting its phosphorylation by cyclin D/CDK4 [3].

In order for a developing neoplasm to persist, it must establish mechanisms to evade host tumor suppression and promote aberrant cell survival. Two such tumor suppression pathways include the p53 pathway and the Bcl-2 pathway. Uveal melanomas overexpress Bcl-2, a molecule that blocks the release of mitochondrial cytochrome C and the activation of pro-apoptotic caspase proteins [27]. The p53 pathway recognizes a wide variety of oncogenic insults and responds by triggering cell senescence or apoptosis [3]. However, in uveal melanomas a p53 inhibitor, HDM2, is overexpressed resulting in uveal melanoma cell survival [3, 27].

The mitogenic activated protein kinase (MAPK) signalling pathway, associated serine/threonine kinases (i.e., RAS/RAF/ERK/MEK), and the phosphatidylinositol-3-kinase (PI3K)/AKT have also been implicated in the development of various cancers, including uveal melanoma [1, 3, 28, 29]. In contrast to cutaneous melanomas, uveal melanoma lacks a mutation in the *BRAF*, *NRAS*, or *KIT* genes that influence MAPK signalling, suggesting that the two forms of melanoma occur via differing pathogenic pathways [1, 29]. Recent studies have demonstrated that mutations of the *GNAQ*, *GNA11*, *PLCB4*, and *CYSLTR4* genes that encode members of the heterotrimeric G-protein alpha subunits may result in their constitutive G-protein activation and upregulation of the MAPK pathway in uveal melanoma [1, 30–33]. There is also evidence that the PI3K/AKT pathway, a commonly altered signalling pathway in human tumors, is also altered in uveal melanoma. The PI3K/AKT pathway is a cell survival mediator, and is negatively regulated by the tumor suppressor PTEN. PTEN is downregulated in uveal melanoma, promoting tumor cell survival [3, 27, 29]. The RAF/ERK/MEK and PI3K/AKT pathways are also activated by the insulin-like growth factors (IGFs) through their interaction with the insulin-like growth factor-1 receptors (IGFR1). IGFR1 is upregulated in many uveal melanomas, resulting in cell survival and unregulated growth [3].

An inactivating somatic mutation of the BRCA-1 associated protein (BAP1) has been implicated in the progression of uveal melanoma, as the mutation is present in 84% of metastasizing tumors. Germline mutations in BAP1 have been observed in 5% of uveal melanomas and have been associated with larger tumor size and ciliary body involvement.

Two recurrent mutations that are associated with a positive prognosis have been identified in patients with primary uveal melanoma. The first is a recurring mutation occurring at codon 625 of the *SF3B1* gene, which encodes the splicing factor 3B subunit 1. SF3B1 mutations and BAP1 mutations are nearly mutually exclusive, suggesting that they may represent alternative pathways in tumor progression [34]. The second mutation associated with a positive prognosis is a mutation in eukaryotic translation initiator factor 1A (EIF1AX), which results in an in-frame alteration at the N-terminus of the protein [35].

The molecular changes discussed above are observed in metastatic and non-metastatic uveal melanomas, implying that these changes occur early in the evolution of the primary tumor. Later changes occur nearly mutually exclusively in either non-metastatic tumors (i.e., gain of chromosome 6p) or in metastatic tumors (i.e., monosomy 3) and represent a bifurcation in tumor progression [36–38]. Generally, monosomy 3 has been closely associated with metastasis and mortality [39]. The greater metastatic potential of cells bearing the chromosome 3 monosomy may be due to the loss of specific tumor suppressor genes [40, 41]. Karyotype analysis suggests that this chromosome 3 aneuploidy is an early event in metastasis, followed by secondary chromosomal changes, including chromosome 8 gain (40% of uveal melanomas) and the loss of the q arm of chromosome 6 (25% of uveal melanomas) [42–44]. Mortality risk is greater when chromosome 3 loss and chromosome 8 gain co-occur, as is usually the case. Conversely, chromosome 6p gain is associated with a more favorable prognosis, apparently

delaying or preventing chromosome 3 loss and delaying metastatic death in the presence of concurrent chromosome 3 loss [24–26].

These findings derived from primary uveal tumors have allowed us to identify a gene expression profile that is highly accurate for identifying patients at increased risk for metastatic disease [45, 46]. The development of a clinically practical platform for analyzing gene expression profiles would benefit those patients at high risk for metastatic disease by strengthening surveillance efforts, permitting earlier treatment, and facilitating the enrollment of suitable patients into ongoing clinical trials [45]. These genes are analyzed using a robust, but clinically feasible, PCR-based gene assay. Studies have demonstrated that assays may be performed accurately on fine-needle aspirate biopsy, even though the RNA quantity may be below detectable limits. These assays enhance prognostication efforts, while also guiding future patient management [45].

Apart from the molecular changes outlined above, uveal melanomas also experience microscopic and macroscopic changes. Uveal melanomas are capillary-rich tumors that often display a phenomenon called "vascular mimicry" [27, 47]. This process involves intratumoral channels composed of a PAS-positive basement membrane, devoid of endothelial cells. Although the function of these structures is currently unknown, the presence of these intratumoral channels, high vascular density, and the invasion of tumor cells into these blood vessels and sclera are unfavorable prognostic factors [27, 47–49]. Metastasis occurs exclusively by hematogenous spread, as there is no lymphatic drainage of the ocular interior. Uveal melanomas often demonstrates a strong hepatic tropism [3]. The uveal melanoma cells can produce a variety of factors that promote angiogenesis, invasion, and metastasis (e.g., metalloproteinases, fibroblast growth factor, adhesion molecules, vascular endothelial growth factor, etc.) [27, 50–52].

CLINICAL PRESENTATION

Intraocular tumors generally present with associated visual symptoms or are detected as an incidental finding on clinical exam.

Most uveal melanomas are of choroidal origin (90%) [6]. Choroidal melanoma appears as a mass deep to the retina, without retinal feeder vessels, and often produces retinal detachment (Fig. 1). Occasionally, vitreous hemorrhage may occur, obscuring visualization of the tumor. In these instances, the tumor is only visible on ocular ultrasonography [5]. Choroidal melanomas may present as pigmented (55%), non-pigmented (15%), or mixed (30%) [13]. Choroidal melanomas appear in one of three configurations: dome (75%), mushroom (20%), which involves the tumor breaking through the Bruch membrane and herniating into the subretinal space, or diffuse (5%), which are flat lesions often mistaken for choroidal nevus. The mean basal dimension of a choroidal melanoma is 11.3 mm and the mean thickness is 5.5 mm [53]. Choroidal melanomas are classified clinically on the basis of thickness: small (0–3.0 mm), medium (3.1–8.0 mm), and large (8.1 mm or greater) [5].

The second most common form of uveal melanoma, ciliary body melanoma (Figs. 2, Fig. 3), is rarely diagnosed as a single entity as it often presents with associated iris or choroidal melanoma due to local extension. Ciliary body melanoma typically presents with prominent episcleral (sentinel) vessels, shallowing of the anterior chamber, unilateral lens changes, unilateral decreased or increased intraocular pressure, a large nodular ciliary body mass, and occasionally, extraocular extension [54]. The ciliary body melanoma can be observed biomicroscopically as a variable pigmented lesion mass with diffuse, nodular, or mixed pattern situated behind the pupil. Macroscopically, choroidal melanomas are classified on the basis of diameter, with larger diameters being associated with a poorer 5-year prognosis: small type (less than 11 mm), medium type (11–15 mm), and large type (greater than 15 mm) [55].

Iris melanoma occurs far less often than uveal melanomas of the posterior segment of the eye (i.e., choroid and ciliary body). Classically, the iris melanoma presents as a gradually expanding pigmented mass (an asymptomatic finding in the large majority), with a consistently demonstrated predilection for the

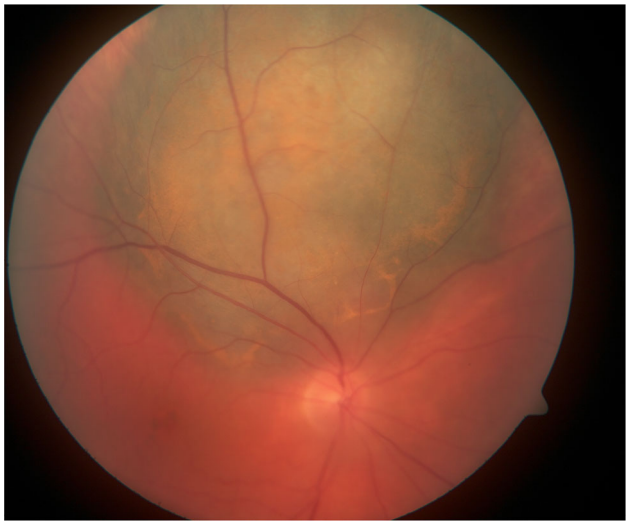

Fig. 1 Fundoscopic image of choroidal melanoma

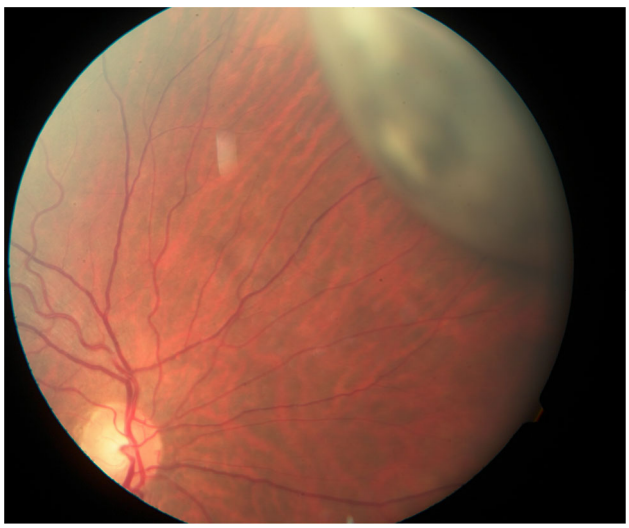

Fig. 2 Fundoscopic image of ciliary body melanoma

inferior iris (Figs. 4 and 5) [56]. Most iris melanomas have some degree of pigmentation, oftentimes a brown or yellow color. The mean basal dimension of an iris melanoma is 6.0 mm and the mean thickness is 2.0 mm [57]. The majority of melanocytic tumors of the iris are either benign nevi or freckles and tend to remain stable over time. However, tumor growth is not always a sign of malignant degeneration into melanoma [58]. The diagnosis of iris melanoma can only be definitively made by microscopic confirmation. The clinical features that prompt an excisional biopsy include large tumor size, prominent tumor vascularity, tumor seeding, elevated intraocular pressures, and tumor-related ocular complications (e.g., hyphema) [57].

DIAGNOSIS AND PROGNOSIS OF UVEAL MELANOMA

Uveal melanoma is diagnosed through fundoscopic examination by an experienced clinician,

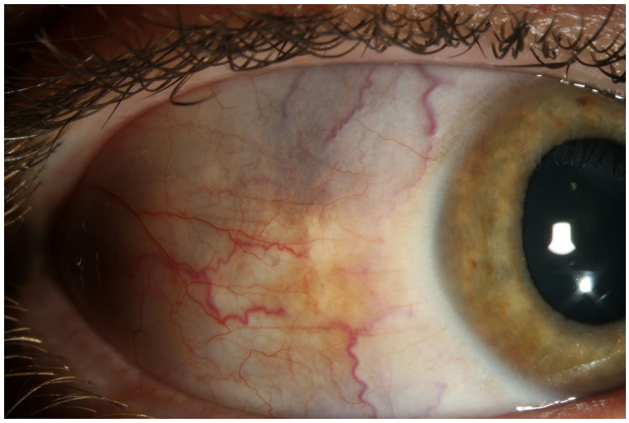

Fig. 3 Gross image of ciliary body melanoma with sentinel vessels

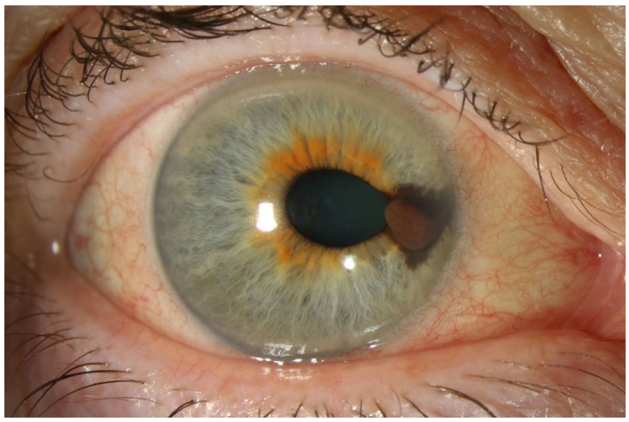

Fig. 4 Gross image of iris melanoma

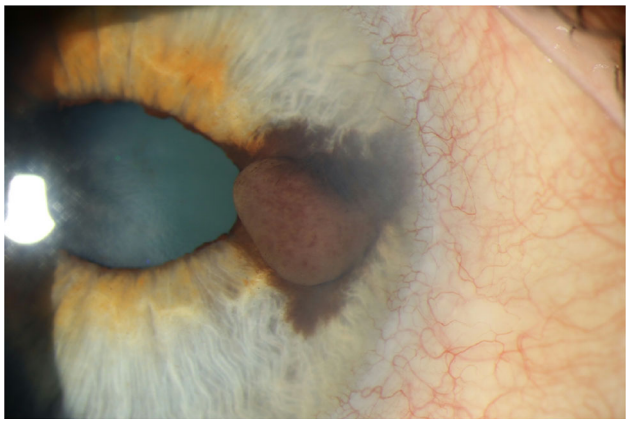

Fig. 5 Gross image of iris melanoma

followed by further characterization using a number of ancillary tests [5]. These ancillary tests include ultrasonography, fluorescein angiography, indocyanine green angiography, enhanced depth imaging optical coherence tomography, autofloresence, and fine-needle

aspiration biopsy. Cytogenetic analysis of melanoma using DNA or RNA methods can add to the prognostication of uveal melanoma (i.e., mutations in chromosomes 3, 6, and 8; see "Pathogenesis") [5].

The long-term prognosis of uveal melanoma is poor with death occurring in 50% of cases [59]. Approximately half of patients with uveal melanoma will experience metastasis within 10 years of diagnosis, irrespective of type of treatment received [12, 60–64]. The median survival after metastasis is 6–12 months; however, the median survival of patients receiving treatment is better than those not receiving treatment [59].

The prognosis of uveal melanoma can be estimated by clinical, histopathological, and cytogenetic markers. The most effective measure to minimize poor prognosis is early detection of melanoma when the tumor is small and at lowest risk for metastatic disease [59]. As a result, systemic monitoring is imperative in patients diagnosed with uveal melanoma because of risk of metastasis to the liver, lung, and skin. It is therefore advised that patients undergo physical examination and liver function tests twice yearly and annual chest radiograph and liver imaging (either MRI or ultrasound) [5].

Poor prognosis with uveal melanoma includes several factors, including older patient age, tumor location in the ciliary body, large tumor size, increasing tumor thickness and diameter, presence of subretinal fluid, pigmented melanoma, diffuse (flat) configuration, extraocular extension, epithelioid cell type, increased mitotic activity, infiltrating lymphocytes, tumor vascular networks, chromosomal mutations (e.g., involving chromosomes 3, 6, and 8), and ocular melanocytosis [53, 59, 65, 66].

The 5- and 10-year rates of metastasis, stratified on the basis of type of uveal melanoma (i.e., iris, ciliary body, and choroid), can be found in Table 1. The lower metastasis rate of iris melanoma is related to its lower biologic activity or smaller tumor size [53, 67]. Whereas, the poor prognosis of ciliary body melanoma has been related to larger tumor size, predilection for monosomy 3 and 8q gain, and tumor microvascular patterns [39, 67–69].

Table 1 5- and 10-year rates of metastasis, stratified on the basis of type of uveal melanoma

Type of melanoma	5-year metastatic rate (%)	10-year metastatic rate (%)
Iris	4	7
Ciliary	19	33
Choroid	15	25

Based on information gathered from Kaliki et al. [59]

The American Joint Committee on Cancer Staging Manual (AJCC) 7th edition provides a detailed classification of posterior (ciliary body and choroid) uveal melanoma into defined anatomical and prognostic groups. There are no prognostic stages for iris melanoma in this manual [70].

The AJCC classification for posterior uveal melanoma involves grading tumors on the basis of size via a combination of basal diameter and thickness, labeled as T1, T2, T3, and T4. Tumors in each category can be further subclassified on the basis of the presence or absence of ciliary body involvement and extraocular extension (EOE) [71].

DIFFERENTIAL DIAGNOSIS

Lesions that are misdiagnosed as melanomas are referred to pseudomelanomas [72]. Although many of these pseudomelanomas are benign, many of these lesions have the potential to cause a serious threat to vision, undergo malignant transformation, or in some cases may be the harbinger of neoplasm elsewhere. Therefore, it is vital that such lesions be identified appropriately, not only to avoid inappropriate treatment but also to ascertain that these lesions be treated appropriately and in a timely manner [72].

The list of lesions that mimic uveal melanomas is extensive. A study conducted by Shields et al. identified 40 different conditions at final diagnosis in 400 different patients who had been referred with a pseudomelanoma [73].

Some lesions occur more frequently than others, as evidenced by a study that examined the incidence of pseudomelanomas within 1200 patients with a presumed diagnosis of uveal melanoma, during a 25-year period. In 1739 of the patients (14.5%) a final diagnosis different from uveal melanoma was made; the most common pseudomelanomas included choroidal nevus (49%), peripheral exudative hemorrhagic chorioretinopathy (PECHR; 8%), congenital hypertrophy of the retinal pigment epithelium (CHRPE; 6%), idiopathic hemorrhagic detachment of the retina or retinal pigment epithelium (5%), circumscribed choroidal hemangioma (5%), and age-related macular degeneration (4%) [74]. The most common pseudomelanoma identified in the study, choroidal nevus, can have a remarkably similar appearance to choroidal uveal melanoma. Melanoma can be distinguished from a nevus on the basis of risk factors and the fact that melanomas show growth over time, while nevi are stable over time [5].

Pseudomelanomas can be divided into pigmented and non-pigmented lesions (Table 2). Pigmented lesions may be of melanocytic origin or may originate from the iris, ciliary body, or retinal pigmented epithelium. Non-pigmented lesions are more disparate and can be divided into neoplastic, vascular, and inflammatory or reactive [72].

Table 2 Classification of pseudomelanomas of the choroid

Pigmented lesions	
Melanocytic derived	Examples: nevus, melanocytoma, metastasis, indeterminate melanocytic lesions, and bilateral diffuse uveal melanocytic proliferation
Retinal pigmented epithelium derived	Examples: adenoma, combined hamartoma, reactive hyperplasia, and congenital hyperplasia of the retinal pigmented epithelium
Non-pigmented lesions	
Neoplasm	Primary: e.g., hemangioma and osteoma
	Secondary: e.g., metastasis and lymphoreticular
Non-neoplasm	Vascular: e.g., disciform, retinal vasoproliferative tumors
	Inflammatory: e.g., scleritis and tuberculosis

Based on information gathered from Rennie [72]

TREATMENTS

Local Tumor Control

Ocular treatment in uveal melanoma is necessary to prevent metastasis of the primary tumor and for the preservation of vision. Treatment strategies depend on the extent of disease, condition of the eye, spread to distant sites of metastasis, and patient's thoughts and wishes. For asymptomatic patients with smaller tumors (< 2.5 mm height and less than 10 mm in the largest basal dimension), observation for growth before the administration of treatment is recommended [75, 76]. However, there is great contention surrounding this clinical approach. As discussed by Shields et al. [77], of small choroidal melanocytic tumors measuring 3 mm or less in thickness at initial examination, 18% demonstrated growth and 3% metastasized at follow-up. On the basis of their analysis, clinical features of the tumor could be used to predict tumor growth and metastasis, as well as ultimately guide management. Factors predictive of tumor growth include greater tumor thickness (greater relative risk (RR) for initial tumor thickness of 2.1–3.0 mm (RR 5.2) and tumour thickness of 1.1–2.0 mm (RR 4.3) vs. < 1.0 mm in thickness), posterior tumor margin in contact with the optic disc, symptoms of flashes and floaters, blurred vision, orange pigment on tumor surface, and presence of subretinal fluid. Factors predictive of tumor metastasis included posterior tumor margin in contact with optic disc, documented growth, and greater tumor thickness (relative risk for metastasis was greatest for tumor thickness of 1.1–3.0 mm, RR 8.8).

The results of this analysis suggest that there may be a valid argument for the active treatment vs. observation of precursor lesions with high-risk clinical features [77].

In those patients with larger tumors and those with symptoms, active treatment is recommended [78]. The major strategies for local tumor control can be subdivided into surgical procedures and radiation therapy (RT).

Surgical options include enucleation (eye removal), orbital exenteration, endoresection, and exoresection [79]. Enucleation is employed in certain circumstances, including in those patients with a clinical diagnosis of uveal melanoma, a tumor that involves more than 40% of the intraocular volume, eyes with neovascular glaucoma, and medium to large uveal melanomas [79, 80]. If the tumor extends into the orbit, orbital exenteration, a more extensive resection that involves the removal of all orbital contents, and adjuvant external beam radiation are commonly employed [79]. In contrast to enucleation and orbital exenteration, endoresection and exoresection are designed to maintain visual functioning of the eye and preserve ocular cosmesis [81]. Endoresection, also called "transretinal resection", remains controversial because of fears regarding iatrogenic dissemination that may result in local recurrence and metastatic disease [82, 83]. However, long-term follow-up studies have demonstrated that endoresection has local tumor recurrence rates similar to proton beam radiotherapy and plaque brachytherapy (less than 5%) [81, 82]. In initial studies, exoresection (also called eye wall resection or trans-scleral resection) was associated with increased rates of local tumor recurrence when compared to radiotherapy (recurrence rate of 6–57%) [83, 84]; however, with the addition of postoperative ruthenium plaque radiotherapy, local treatment failure rates have fallen considerably (to 5–10%) [81–83]. The role of surgical procedures in the treatment of uveal melanoma remains controversial because of fears of tumor cells being disseminated hematologically during surgery and a failure to demonstrate a difference in survival outcomes when compared to RT [82, 85].

RT of uveal melanoma allows for local tumor control, sparing of vision, and conservation of the globe [79]. Radiation is hypothesized to affect the viability of uveal melanoma cells via lethal chromosomal injury, damage to the tumor vasculature, and the induction of reactive oxygen species. RT may be delivered through various modalities, including charged particle therapy (CPT), episcleral radioactive plaque, stereotactic external beam irradiation (SEBI), or transpupillary thermotherapy [86]. CPT involves the use of charged particles (i.e., protons, helium ions, or carbon ions) that are fired with a specific kinetic energy. The particles will enter the tissue and emit the majority of their energy at a fixed depth (i.e., the Bragg peak); little radiation dose is delivered past this point. The depth of the Bragg peak can be altered by changing the initial kinetic energy of the particles. This allows for the delivery of a large dose of radiation to a small volume of tissue [87]. Of all the eye-conserving forms of treatment, CPT is associated with the lowest overall risk of tumor recurrence (local recurrence 3.5% at 5 years, 5% at 10 years) [88, 89]. Apart from CPT, episcleral radioactive plaque, or brachytherapy, is also a commonly used RT. This treatment involves two invasive surgical procedures in which a plaque containing a radioactive material is placed over the region of the tumor (guidelines suggest placing the plaque such that it overlaps the entire tumor margin by at least 2 mm) and later removed after the prescribed dose is delivered [86, 87, 90–92]. The radioisotopes that are most commonly used in this procedure are iodine-125, palladium-103, and ruthenium-106 [87]. The COMS reported a 10% recurrence rate at 5 years after iodine-125 plaque brachytherapy [93]. Finally, transpupillary thermotherapy and SEBI are newer treatment modalities that are becoming increasingly accepted as effective methods of achieving local tumor control. Transpupillary thermotherapy involves delivering an infrared beam of light energy into an intraocular neoplasm, resulting in tumor cell necrosis. Despite its advantages (i.e., precision and immediate necrosis of the neoplasm), initial enthusiasm has been dampened by reports of substantial visual loss and local tumor

recurrence [94]. This method is a useful primary treatment in a limited group of patients (i.e., small choroidal melanomas near the optic disc or fovea) owing to its precision; however, in most instances this method is best employed as a secondary treatment to plaque radiotherapy [94]. SEBI involves the delivery of a single or several doses of radiation to a well-circumscribed target volume, thus reducing the effects of radiation on the surrounding tissue [95]. This modality of treatment is often utilized in instances where plaque brachytherapy is deemed unsuitable because of large-sized or peripapillary or posteriorly located tumors. The long-term complications associated with SEBI are similar to those observed in CPT and plaque brachytherapy [95]. The choice of RT must optimize dose distribution, while minimizing treatment morbidity, as the radiation dose necessary to control uveal melanoma often exceeds the tolerance of orbital components [79].

Locoregional Treatments of Liver Metastasis

Liver metastasis remains the leading cause of morbidity and mortality in patients with advanced uveal melanoma. Locoregional treatments that aim to control liver metastasis include surgical resection, hepatic intra-arterial chemotherapy (HIA), isolated hepatic perfusion, and percutaneous hepatic perfusion. Most of the evidence for these treatments is based on small, non-comparative, single-institution studies.

There are currently no randomized controlled trials that have compared hepatic resection with best supportive care or chemotherapy. Six of the studies examined included a nonsurgical comparator group. Studies including a nonsurgical comparator group have demonstrated a larger median duration of survival with hepatic resection versus nonsurgical care (i.e., 14–24 vs. 3–12 months, respectively) [96–99]. Prolonged overall survival times were also demonstrated in non-comparative studies of hepatic resection (range 19–34 months) [100–105]. Most studies reported a 5-year overall survival rate in excess of 20% (range 0–42%) [98, 100–103]. Studies have also consistently demonstrated that negative margin resection, long disease-free survival, low number of lesions, and limited disease distribution are significant positive prognostic indicators [97–101, 104].

Postsurgical recurrence was common, with reported recurrence rates of 72–75% in patients with metastatic melanoma after hepatic resection [102, 103]. Although these findings are suggestive of a survival benefit from surgery, it must be noted that surgical resection is found to be feasible in less than 10% of uveal melanomas metastatic to the liver. Limiting factors include too many metastatic foci, tumors in difficult locations, insufficient hepatic reserve, and tumors invading blood vessels [22].

In HIA, catheters are placed into the hepatic artery either surgically though the gastroduodenal artery or percutaneously through the femoral artery, followed by infusion of chemotherapy (most commonly fotemustine, cisplantin, or melphalan) [106–108]. The European Organization for Research and Treatment of Cancer (EORTC) 18021 study, a randomized phase 3 trial, HIA was compared to intravenous delivery of fotemustine in patients with previously untreated, unresectable liver-only metastases from ocular melanoma [109]. Although the study found an improved overall response rate with HIA compared with intravenous fotemustine (11% vs. 2%, respectively), the study failed to demonstrate a difference between the two groups with respect to overall survival. Several non-comparative studies have documented response rates ranging from 16% to 36% and median overall survival durations ranging from 9 to 21 months [107, 108, 110–112]. However, it is important to note that several of these studies included patients with extrahepatic disease. HIA is not a treatment free of complications, as the placement of catheters in HIA is associated with a risk of thrombosis, infection, leakage, and displacement [107, 111–113].

Hepatic arterial embolization is a technique used to deliver high-dose chemotherapy directly to liver tumor cells, while providing select ischemia. Most studies investigating

hepatic arterial embolization utilize the transarterial chemoembolization (TACE) procedure and various chemotherapeutic agents (e.g., fotemustine, cisplantin, and 1,3-bis(2-chloroethyl)-1-nitrosourea) followed by the administration of an embolizing agent [114–118]. In these studies response rates ranged from 0% to 39%, and median overall survival ranged from 5.0 to 8.9 months. Key prognostic factors in TACE treatment include the degree of liver involvement (with more extensive liver involvement being associated with poorer overall median survival durations), baseline lactate dehydrogenase level, and the number of additional visceral sites involved [115–117]. In an effort to incite a systemic immune response against tumor cells and improve patient outcomes, Sato et al. performed transaterial embolization with granulocyte macrophage colony-stimulating factor (GM-CSF) in patients with metastatic ocular melanoma limited to the liver [114]. A median overall survival time of 14.4 months was reported. A randomized phase 2 trial comparing immunoembolization with GM-CSF versus bland embolization found that immunoembolization induced more robust inflammatory reactions, which in turn were correlated with delayed progression of extrahepatic systemic metastasis [119].

Isolated hepatic perfusion (IHP) is a surgical procedure that involves isolating the hepatic circulation, and thus allowing the delivery of high doses of chemotherapy directly to the liver [106, 120]. Alkylating agents are favored in this form of therapy, as they are effective over a relatively short exposure time and have steep dose–response curve [121]. The most frequently evaluated agent in patients with hepatic metastatic uveal melanoma is melphalan. Noncomparative studies of IHP treatment of hepatic metastases from uveal melanoma have reported response rates ranging from 33% to 62% and a median overall survival ranging from 10 to 12 months [122–124]. Despite these promising results IHP is a complicated procedure with several shortcomings. The procedure is lengthy, non-repeatable, and associated with high morbidity and long hospital stays [122–124].

A nonsurgical alternative to IHP has been developed, which is both less complicated and repeatable. The procedure, termed percutaneous hepatic perfusion (PHP), involves inserting a double-balloon catheter in the inferior vena cava to isolate hepatic venous blood. The liver is infused with chemotherapeutic agent, the venous effluent is then filtered extracorporeally before being returned to the systemic circulation via the jugular vein [106]. A recent randomized phase 3 study compared repeated PHP delivery of melphalan (every 4–8 weeks) to best alternative care (BAC) in patients with unresectable hepatic metastases from ocular and cutaneous melanoma. The study found that the median hepatic progression-free survival was significantly prolonged PHP compared to BAC (7.0 vs. 1.6 months, respectively). Although median overall survival did not differ significantly between the PHP and BAC groups (10.6 vs. 10.0 months, respectively), it is likely that this analysis was confounded by patient crossover from the BAC arm to the PHP arm after hepatic progression [125].

Systemic Therapies

Although several novel systemic therapies for patients with metastatic cutaneous melanoma have been shown to be efficacious in randomized trials (i.e., phase 2 and phase 3) and have received US Food and Drug Administration (FDA) approval, the situation for patients with metastatic uveal melanoma is quite different [106]. Several chemotherapeutic and immunomodulatory agents have been examined in patients with uveal melanoma; however, response rates have been low (less than 5%), with median overall survival ranging from 6 to 14 months [126–137].

A recent phase 2 clinical trial compared the efficacy of chemotherapy versus selumetinib, a selective, non-ATP competitive inhibitor of MEK1 and MEK2, in patients with advanced uveal melanoma. Selumetinib compared with chemotherapy resulted in a modest improvement in progression free-survival (15.9 vs. 7 weeks, respectively; $p < 0.001$) and response rate (14% partial response vs. 0% response in accordance with Response Evaluation Criteria in Solid Tumors, respectively). However, no

improvement in overall survival was observed [138]. Unfortunately, a phase 3 study of selumetinib in combination with dacarbazine for the treatment of metastatic uveal melanoma did not meet its primary end point of progression-free survival. A full evaluation of the data is ongoing [139].

Another recent study examined the clinical outcomes of patients with stage IV uveal melanoma treated with programmed death receptor 1 (PD-1) and PD-1 ligand (PD-L1) antibodies. The overall response rate was found to be 3.6%. The study concluded that PD-1 and PD-L1 antibodies rarely confer durable remission in patients with metastatic uveal melanoma [140].

Studies examining novel targeted agents are currently underway.

CONCLUSIONS AND FUTURE DIRECTIONS

Uveal melanoma is a complex condition that requires a multidisciplinary approach to management and treatment. Early detection and therapy are important factors in disease survival. Therefore, it is imperative that the treating physicians be familiar with the clinical features of uveal melanoma to distinguish it from mimickers and to provide effective and timely treatment.

Current treatment strategies are based on single-center case series examining individual therapies. The rarity of uveal melanoma has made patient enrollment in clinical trials difficult. This is compounded by a lack of uniformity in institutional data collection, which makes comparison across institutions difficult. There is a need for standardization in data collection and collaboration across institutions to better evaluate current and future treatments.

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