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REVIEW

Uveal melanoma: relatively rare but deadly cancer

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Abstract

Although it is a relatively rare disease, primarily found in the Caucasian population, uveal melanoma is the most common primary intraocular tumor in adults with a mean age-adjusted incidence of 5.1 cases per million per year. Tumors are located either in iris (4%), ciliary body (6%), or choroid (90%). The host susceptibility factors for uveal melanoma include fair skin, light eye color, inability to tan, ocular or oculodermal melanocytosis, cutaneous or iris or choroidal nevus, and BRCA1-associated protein 1 mutation. Currently, the most widely used first-line treatment options for this malignancy are resection, radiation therapy, and enucleation. There are two main types of radiation therapy: plaque brachytherapy (iodine-125, ruthenium-106, or palladium-103, or cobalt-60) and teletherapy (proton beam, helium ion, or stereotactic radiosurgery using cyber knife, gamma knife, or linear accelerator). The alternative to radiation is enucleation. Although these therapies achieve satisfactory local disease control, long-term survival rate for patients with uveal melanoma remains guarded, with risk for liver metastasis. There have been advances in early diagnosis over the past few years, and with the hope survival rates could improve as smaller tumors are treated. As in many other cancer indications, both early detection and early treatment could be critical for a positive long-term survival outcome in uveal melanoma. These observations call attention to an unmet medical need for the early treatment of small melanocytic lesions or small melanomas in the eye to achieve local disease control and vision preservation with the possibility to prevent metastases and improve overall patient survival.

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Introduction

Melanoma is a relatively rare tumor arising from melanocytes located at various anatomic locations, including skin, mucous membrane (nasal mucosa, oropharyngeal, pulmonary, gastrointestinal, vaginal, anal/rectal, urinary tract), ocular region (uvea, conjunctiva, eyelid, orbit), and rarely from unknown primary sites.[1] In a review of 84 836 cases from the National Cancer Database, including cases diagnosed between 1985 and 1994, the percentages of melanomas arising from the skin, eye and adnexa, mucosa, and unknown primaries were 91%, 5%, 1%, and 2%, respectively.[1]

Among ocular melanomas, 83% arise from uvea, 5% from conjunctiva, and 10% from other sites.[1] The most common site for uveal melanoma is the choroid. In a study of 8033 patients with uveal melanoma by Shields *et al*,[2] the tumor was located in the iris in 285 (4%), ciliary body in 492 (6%), and choroid in 7256 (90%) cases. In this report, we discuss the epidemiology, diagnosis, treatment, and prognosis of uveal (iris, ciliary body, and choroidal) melanoma. We also discuss the importance of early detection and potential new treatments.

Incidence of uveal melanoma

Analysis of the Surveillance, Epidemiology, and End Results (SEER) program database of the United States National Cancer Institute over a 36-year period between 1973 and 2008, including 4070 patients with primary uveal melanoma, revealed an overall mean age-adjusted incidence of uveal melanoma at 5.1 cases per million per year.[3] Similarly, analysis of data from the European Cancer Registry-based study on survival and care of cancer patients (EUROCARE) in Europe, including 6673 patients with uveal melanoma diagnosed from 1983 to 1994, revealed standardized incidence rates of 1.3–8.6 cases per million per year.[4] In Europe, the incidence of uveal melanoma followed a north-to-south decreasing gradient from a minimum of 2 per million per year in Spain and southern Italy to a maximum of 8 per million per

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year in Norway and Denmark.[4] This north-to-south decreasing gradient is related to the protective effect of ocular pigmentation in the southern populations with respect to higher exposure to ultraviolet light at lower latitudes.[4] The incidence of uveal melanoma is low in Africa and Asia, with an incidence rate of 0.2–0.3 cases per million per year.[5] Across continents, there has been no significant change in the overall incidence of uveal melanoma over the years.[3,4,6,7] Based on region of origin, the number of uveal melanoma cases per year has been estimated per population at 316 for Africans, 857 for Asians, 1154 for Hispanics, and 4351 for White non-Hispanics.[5]

The next sections include discussions of the various characteristics studied in diagnosis of uveal melanoma: age, gender, and race, followed by a discussion of the factors that increase the likelihood of developing uveal melanoma.

Age

Uveal melanoma is more commonly seen in older age groups, with a progressively rising age-specific incidence rate that peaks at age 70 years, and plateaus after 75 years.[3,4,8,9] Uveal melanoma in children is rare, and congenital uveal melanoma is extremely rare.[9–11] In a study of uveal melanoma in children and teenagers, age at presentation was 0 to 5 years in 3%, 5.1 to 10 years in 11%, 10.1 to 15 years in 35%, and 15.1 to $\leq$20 in 50%.[10] The age-specific incidences of uveal melanoma per million population[9] are listed in Table 1.

In the United States and Europe where there is a prominent Caucasian population, the median age of uveal melanoma diagnosis is 59 to 62 years.[2,3,8] In a recent study of epidemiological trends in uveal melanoma in 7043 patients from the SEER database over 1973 to 2009, the mean age at diagnosis increased between 1973 (59 years) and 2009 (62 years).[8] This increasing trend was speculated to be related to increasing life expectancy and frequent ocular examinations.[8] However, studies from Asian countries indicate lower age at diagnosis, with mean age of 45 years in Chinese populations, 46 years in Asian Indians, 51 years in Taiwanese, 54 years in Korean, and 55 years in Japanese populations.[5,6,12–15] Similarly, lower age at presentation has been reported in Hispanics at 52 years and in Blacks at 54 years.[16,17]

Table 1 Age-specific incidences of uveal melanoma per million population in the United States

Age (years)	*Males*	*Females*
0–4	0	0
10–14	0.2	0
20–24	0.4	0.6
30–34	1.7	1.7
40–44	3.9	2.4
50–54	10.5	6.5
60–64	14.9	11.7
70–74	24.5	17.8
80–84	23.2	16.1

Adapted from Singh and Topham.[9]

Gender

In population-based epidemiological studies, the age-adjusted incidence of uveal melanoma is higher in males compared with females.[3,4] In an analysis of SEER data, the age-adjusted incidence of uveal melanoma was 5.8 per million in males compared with 4.4 per million in females.[3] In a study including Australian populations, the age-standardized incidence in men was higher (0.83 per 100 000) compared with that in women (0.59 per 100 000) for choroidal melanomas.[18] The difference in incidence between the genders was largely due to significantly higher rates in men 65 years and older. However, there was no significant difference in rates between men and women younger than 65 years.[18] Gender differences in rates in large cohort clinical studies with no age adjustments have not been reported. In fact, a large study of 8033 consecutive patients with uveal melanoma showed that 50% were males and 50% were females.[2]

Race

Uveal melanoma is more common in the White population. The ratio of uveal melanoma in Black : White patients is estimated at 1 : 15 to 1 : 50.[19–21] The relative risk (RR) calculation of uveal melanoma in various racial groups (Black, Asian and Pacific Islander, Hispanic, and non-Hispanic White) in 1352 patients using 1992 to 2000 SEER program data revealed the ratios of Black:Asian: Hispanic:non-Hispanic White at 1 : 1.2 : 5 : 19.[21] The Black : White ratio is influenced by gender at 1 : 42 in male patients and 1 : 12 in female patients, with a greater incidence in males *vs* females (3.5 : 1).[21] In a comprehensive analysis of 8100 consecutive patients with uveal melanoma, the patient race was Caucasian (98%), Hispanic (1%), Asian (<1%), and African American (<1%).[19] Margo *et al*[20] reported that the RR of uveal melanoma for Blacks compared with non-Hispanic Whites was 0.03. The rarity of uveal melanoma in Blacks is probably related to protective effects associated with dark skin pigmentation or unknown cultural–environmental factors.

Predisposing factors

Host susceptibility factors

Skin color, hair color, and ability to tan The host susceptibility factors for uveal melanoma include fair skin, blond hair, light eye color, and inability to tan. Weis *et al*[22] provided a meta-analysis studying the association between host susceptibility factors and uveal melanoma revealed the following factors to be statistically significant: light eye color (RR, 1.75), fair skin color (RR, 1.80), and inability to tan (RR, 1.64). Blond hair was not a statistically significant independent risk factor.[22] The increased occurrence of uveal melanoma in lighter-skinned people and those with light (blue or grey) colored eyes may be related to less melanin being present in the choroid and retinal pigment epithelium, which results in less protection from ultraviolet light, and increased risk of developing uveal melanoma.[22] Uveal melanoma is more common in people who sunburn easily compared with those who tan well, and as with the previous factors, is likely related to light skin color and less melanin in the eye.[22]

Oculodermal melanocytosis Oculodermal melanocytosis represents a congenital pigmentary abnormality with slate-grey pigmentation of the periocular skin, sclera, uvea, orbit, meninges, palate, and tympanic membrane and is an important risk factor for development of uveal melanoma.[23–25] This condition is generally mostly unilateral, and in some cases, the pigmentation is limited only to the eye. Ocular (no eyelid involvement)/oculodermal melanocytosis is 35 times more common in patients with uveal melanoma, and occurs in 0.04% of the White population and ~1.4 to 3% of those with uveal melanoma.[23,25] The estimate of lifetime risk for a Caucasian patient with ocular/oculodermal melanocytosis to develop uveal melanoma is 1 in 400.[24]

Cutaneous, iris, and choroidal nevus An association between uveal melanoma and atypical cutaneous nevi (dysplastic nevi), common cutaneous nevi, and cutaneous freckles has been established. Patients with atypical cutaneous nevi are 4.36 to 10.4 times more likely to develop ocular melanoma than the average population.[26,27]

Iris nevus is a risk factor for uveal melanoma in general and it is a particular risk for iris melanoma, although the rate of transformation of iris nevus into melanoma is not clearly understood.[28] In a study of 175 patients with suspicious iris nevus by Territo *et al*,[29] 8 (5%) lesions showed clinical evidence of growth into iris melanoma at a mean follow-up of 5 years. In a recent study of 1611 patients with iris nevus, only 2% of patients showed transformation of nevus to melanoma.[30] By multivariable analysis, the features predictive of growth included age <40 years, hyphema, inferior tumor location, diffuse flat tumor configuration, ectropion uveae, and feathery, geographic margins. For early detection of iris melanoma, these important predictive factors can be remembered by the mnemonic ABCDEF representing A—age young, B—blood (hyphema), C—clock hour inferiorly, D—diffuse, E—ectropion, and F—feathery margins (Table 2).[30]

Choroidal nevus is a common intraocular lesion, found in ~5% of Caucasians in the United States, according to the National Health and Nutrition Examination Survey.[31] Choroidal nevus is found to be associated with cardiovascular, renal, autoimmune, and occupational risk factors, female reproductive factors, and obesity.[31–33] The estimated annual rate of malignant transformation of a choroidal nevus, based on the premise that all melanomas arise from nevus is mathematically calculated at 1 in 8845.[34] The annual rate of malignant transformation of choroidal nevus gradually increases with age, with the lowest rate of 1 in 269 565 for the youngest age group (15–19 years) and the highest rate of 1 in 3664 for the oldest age group (80–84 years).[34] Risk factors predictive of transformation of choroidal nevus into melanoma include: tumor thickness >2 mm, subretinal fluid, symptoms, orange pigment, margin near disc, ultrasonographic hollowness, and absence of halo or

Table 2 Risk factors for the growth of iris nevus into melanoma

Initial	*Feature*	*Hazard ratio*	*% of patients with tumor growth having this feature*	*% of patients with no tumor growth having this feature*
A	Age ≤ 40 years	3	48	24
B	Blood	9	11	<1
C	Clock hour-inferior	9	96	71
D	Diffuse configuration	14	4	<1
E	Ectropion uveae	4	48	18
F	Feathery margin	3	52	24

Adapted from Shields *et al*.[30]

drusen.[35,36] Shields *et al*,[35,36] developed a mnemonic (TFSOM UHHD) to help practitioners remember the ocular melanoma risk factors. TFSOM UHHD stands for 'To Find Small Ocular Melanoma Using Helpful Hints Daily', representing Thickness, Fluid, Symptoms, Orange pigment, Margin, Ultrasonographic Hollowness, Halo absence, and Drusen absence (Table 3). At 5 years, tumors that display one factor show growth in 38% of cases, and those with two or more factors show growth in over 50% of cases.[35,36]

BAP1 mutation BAP1 (BRCA1-associated protein 1) is a nuclear protein encoded by the tumor suppressor gene located on chromosome 3p21.1. The BAP1 tumor predisposition syndrome is a recently identified hereditary cancer syndrome. The somatic or germline mutation of BAP1 predisposes patients to develop uveal melanoma, malignant mesothelioma, cutaneous melanomas, basal cell carcinoma, and renal cell carcinoma.[37] This mutation is transmitted in a Mendelian manner with 50% of the offspring inheriting the mutation. The malignancies occurring in patients with germline BAP1 mutations are less aggressive compared with patients with the same types of tumors that do not show this mutation.[37] A review of 507 blood samples of patients with uveal melanoma disclosed 25 (5%) with BAP1 polymorphisms, and are associated with larger tumors and higher rates of ciliary body involvement.[38]

Environmental factors

Sunlight exposure Various studies have explored the particular association between ultraviolet light exposure and occurrence of uveal melanoma.[39,40] However, published literature does not unequivocally implicate sunlight exposure as a risk factor for uveal melanoma.[39,40] Some studies suggest that chronic ultraviolet light exposure is an independent risk factor for uveal melanoma, whereas other studies contradict this.[39,40] Shah *et al*[39] provided a meta-analysis of all published reports and demonstrated that chronic ultraviolet light exposure, occupational sunlight exposure, outdoor leisure sunlight exposure, and geographic latitude of birth played minimally significant roles in the development of uveal melanoma. A study from Germany revealed that people with light iris color have increased risk for melanoma if they were exposed to ultraviolet radiation.[40]

Intermittent exposure to artificial ultraviolet light No consistent evidence indicates occupational ultraviolet light exposure as an independent risk factor for uveal melanoma. However, some studies suggest that it is a significant risk factor for arc welders who have an occupational exposure to artificial ultraviolet light.[41,42] Increasing evidence suggests that blue light exposure, as opposed to ultraviolet light exposure, may influence the oncogenesis and progression of uveal melanoma.[43] In a meta-analysis of five case–control studies, it was shown that occupational cooking was associated with increased risk of uveal melanoma in both men and women.[44]

We now discuss uveal melanomas based on anatomical location (iris, ciliary body, or choroid) and the particular clinical features and risk factors.

Iris melanoma

Clinical features

Iris melanoma can be circumscribed (90%) or diffuse (10%).[45,46] Iris melanoma, although much less common, is usually diagnosed 10–20 years earlier than ciliary body or choroidal melanomas.[2,45,46] In most cases, it is an incidental finding due to iris color changes (heterochromia) and pupil distortion (corectopia). Iris melanoma is most commonly located in the inferior quadrant (45%) and causes corectopia (45%), secondary

Table 3 Risk factors for the growth of choroidal nevus into melanoma

Initial	*Mnemonic*	*Feature*	*Hazard ratio*	*% of patients with tumor growth having this feature*	*% of patients with no tumor growth having this feature*
T	To	Thickness >2 mm	2	46	15
F	Find	Fluid	3	39	8
S	Small	Symptoms	2	38	10
O	Ocular	Orange pigment	3	32	6
M	Melanoma	Margin ≤3 mm to disc	2	58	31
UH	Using helpful	Ultrasonographic hollowness	3	57	15
H	Hints	Halo absence	6	98	95
D	Daily	Drusen absence	<1	49	NA

Abbreviation: NA, not available.
Adapted from Shields *et al*[36] and Collaborative Ocular Melanoma Study Group.[101]

glaucoma (35%), angle seeding (28%), ectropion uveae (24%), hyphema (3%), and extraocular extension (3%).[47] Secondary glaucoma occurs because of direct compression of the anterior chamber angle, or tumor invasion of the angle, or accumulation of tumor cells or pigment or pigment-laden macrophages in the trabecular meshwork causing outflow obstruction.[48]

Diffuse iris melanoma has an infiltrative, flat, ill-defined growth pattern with confluent or multifocal iris involvement. The diagnosis of diffuse iris melanoma is challenging and is often delayed. The classic findings of diffuse iris melanoma include acquired hyperchromic heterochromia iridis and ipsilateral glaucoma.[49]

Ring melanoma of the anterior chamber is a distinct rare variant that manifests as circumferential, flat tumor growth confined to the trabecular meshwork and anterior chamber angle structures. It presents as refractory unilateral glaucoma simulating pigmentary glaucoma and can be diagnosed only by gonioscopy and UBM.[50]

Diagnosis

The American Joint Committee on Cancer Classification (AJCC) has classified iris melanoma based on tumor location, tumor size in clock hours, tumor extension to ciliary body, and/or choroid and associated features of secondary glaucoma and extraocular extension[51] (see Table 4).

The diagnosis of iris melanoma is carried out by clinical examination with slit-lamp biomicroscopy. Gonioscopy is a useful adjunct to assess the involvement of the anterior chamber angle. For small tumors, anterior segment optical coherence tomography (AS-OCT) is useful with high-resolution imaging of anterior and lateral surfaces. For large iris melanomas, ultrasound biomicroscopy (UBM) and AS-OCT assist in visualization of the posterior tumor extent. B-scan ultrasonography (USG) is superior to AS-OCT in assessing large pigmented lesions because sound waves penetrate better than light energy.[52] Transillumination also aids in assessing ciliary body involvement. Occasionally, fine-needle aspiration biopsy may be used to confirm diagnosis, especially for small iris melanomas. In an analysis of 100 consecutive biopsies of iris lesions, Shields *et al*[53] showed that adequate sample could be obtained in 99% cases with minimal complications.

The most common differential diagnoses for circumscribed iris melanoma are iris nevus, ocular melanocytosis, leiomyoma, iris metastasis, iris cyst, and inflammatory conditions such as sarcoidosis and juvenile xanthogranuloma.[46] Diffuse iris melanomas must be differentiated from congenital heterochromia, congenital ectropion iridis, diffuse iris nevus, pigmentary glaucoma, melanocytomalytic glaucoma, ocular siderosis, hemosiderosis, and iridocorneal endothelial syndrome.[49]

Treatment

Small iris nevus/melanomas (<3 mm basal diameter) in an asymptomatic patient can be monitored for growth with periodic photographic documentation. Small iris melanoma with documented growth is managed by partial iridectomy (removal of portion of iris), iridotrabeculectomy (removal of a portion of the iris and trabecular meshwork needed if the tumor invades the anterior chamber angle), or iridocyclectomy (removal of a portion of the iris and ciliary body indicated in tumors with ciliary body extension).[45,46] Plaque radiotherapy and proton beam radiotherapy are beneficial for tumors with

Table 4 Iris melanoma based on American Joint Cancer Committee (AJCC 7th edition) classification[a]

Primary tumor (T)	
T1	Tumor limited to the iris
T1a	Tumor limited to the iris ≤3 clock hours
T1b	Tumor limited to the iris ≥3 clock hours
T1c	Tumor limited to the iris with secondary glaucoma
T2	Tumor extending into the ciliary body, choroid, or both
T2a	Tumor extending into the ciliary body, choroid, or both, with secondary glaucoma
T3	Tumor extending into the ciliary body, choroid, or both, with scleral extension
T3a	Tumor extending into the ciliary body, choroid, or both, with scleral extension and secondary glaucoma
T4	Tumor with extrascleral extension
T4a	Tumor with extrascleral extension ≤5 mm in diameter
T4b	Tumor with extrascleral extension ≥5 mm in diameter

[a]Source: Edge *et al*.[51]

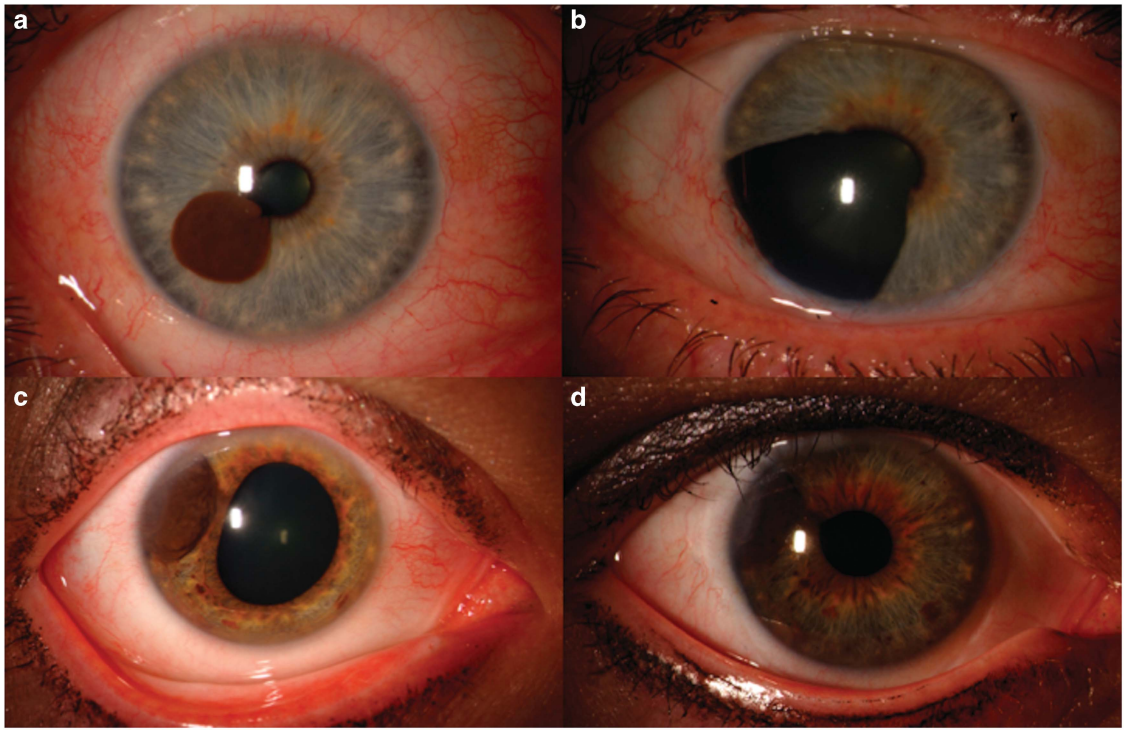

Figure 1 Iris melanoma. (a) Iris melanoma in the mid-zone of iris (b) treated by iridectomy. (c) Iris melanoma at the root of iris and (d) treated with iodine-125 plaque radiotherapy.

extensive tumor seeding and in non-resectable iris tumors, achieving melanoma control in 92% of cases.[49,54,55] (Figure 1). However, vision loss is a worrisome adverse effect of this treatment. Enucleation is indicated for eyes with large tumor, diffuse iris melanoma, eyes with poor initial visual acuity, and those with recurrent tumor.

Prognosis

The prognosis of iris melanoma is better than the prognosis of ciliary body and choroidal melanoma, with five to ten times lower mortality rates.[2,47,56] This may be related to younger age at presentation, smaller tumor size, and less biologic activity.[56] In a review of 317 patients with iris melanoma, metastasis occurred in 4% of patients, and 2% of patients died because of metastasis during a mean follow-up period of 53 months.[47] Kaplan–Meier estimates of metastasis and death at 10 years were 9% and 3%, respectively.[47] The prognostic factors for a worse outcome included increasing age at diagnosis, secondary glaucoma, increased tumor thickness, posterior tumor margin at iris root or anterior chamber angle, and extraocular tumor extension.[2,47,57]

Ciliary body melanoma and choroidal melanoma

The symptoms of ciliary body and choroidal melanoma include blurred vision (38%), photopsia (9%), floaters (7%), visual field loss (6%), visible tumor (3%), pain (2%), metamorphopsia (2%), and 30% of patients are asymptomatic.[58] Ciliary body melanoma is often diagnosed late as the lesion remains hidden behind the iris, and the patient seldom has any clinical symptoms until the lesion is large. Consequently, when the tumors are eventually diagnosed, they present as fairly large with a mean basal diameter of 11.7 mm and tumor thickness of 6.6 mm.2 Ring melanoma of the ciliary body is a rare distinct entity (0.3% of all uveal melanomas) in which the tumor extends circumferentially involving the entire ciliary body, often without any nodular component.[59]

Choroidal melanoma presents as a dome-shaped mass (75%) or has a mushroom configuration because of rupture of Bruch's membrane (19%), and rarely presents as a diffuse variant (6%). The lesion can be pigmented (55%), nonpigmented (15%), or has a mixed color (30%), associated with retinal detachment (71%), intraocular hemorrhage (10%), or extraocular extension (3%).[2] In a review of 7256 cases of choroidal melanoma, the mean basal diameter was 11.3 mm and mean tumor thickness was 5.5 mm.[2]

Diagnosis

The AJCC classifies ciliochoroidal melanoma based on tumor basal dimension, tumor thickness, ciliary body involvement, and associated extraocular extension[51] (Table 5). Diagnosing small ciliary body melanoma is challenging as the melanoma location impedes the ability to visualize it directly. Most cases are detected when the tumors are large with iris or choroidal invasion. Gonioscopy can detect involvement of the anterior chamber angle. Fundus examination with good indentation can help visualize some ciliary body melanomas. Shadowing on transillumination is detected in larger lesions. Conventional USG is a useful adjunct for larger tumors. Recently, high-frequency UBM is recognized as a valuable tool in the detection and follow-up of small ciliary body melanomas (<4 mm), which other conventional techniques would otherwise not detect.[52]

The mainstay of diagnosis of choroidal melanoma is a detailed fundus evaluation with indirect ophthalmoscopy. Serial fundus photography helps monitor these lesions. Small choroidal melanomas can be detected by enhanced depth imaging optical coherence tomography (EDI-OCT), which is particularly useful in lesions <3 mm in greatest dimension, and might be missed using routine diagnostic methods.[60] Small choroidal melanomas are seen as dome-shaped lesions with smooth surface tomography, shaggy photoreceptors, and subretinal lipofuscin deposits and shallow subretinal fluid.[60] EDI-OCT is also a useful tool for differentiating choroidal nevus from small choroidal melanoma; however, it has limited use in diagnosing tumors with thickness >3 mm. It also has limited use with heavily pigmented tumors, which cast a significant posterior shadow.

USG is an important diagnostic tool used to define tumor extent and shape, and to measure tumor dimensions of ciliary body/choroidal melanoma. Typical features of a posterior uveal melanoma on USG include acoustic hollowing, choroidal excavation (42% to 65%), and orbital shadowing.[61,62] Spontaneous vascular movement (69–70%) may be noted in a highly vascularized tumor. Ossoinig[62] described four cardinal acoustic hallmarks of malignant melanoma on A-scan including a regular internal structure with similar height of the inner tumor spikes or regular decrease in height (positive angle kappa sign), low to medium reflectivity, solid consistency with no after movement of tumor spikes, and echographic sign of vascularization with a fast, spontaneous, continuous, flickering vertical motion of single tumor spikes. Fluorescein angiography (FFA) and indocyanine green (ICG) angiography have limited use in choroidal melanoma. The characteristic features on FFA include gradually increasing fluorescence that starts

Table 5 Posterior uveal melanoma based on American Joint Cancer Committee (AJCC 7th edition) classification[a]

Primary tumor (T)	*Tumor dimensions (mm)*	*Ciliary body involvement*	*Extraocular extension*
T1		Yes or no	Yes or no
T1a	Tumor base <3–9 mm with thickness ≤6 mm Tumor base 9.1–12 mm with thickness ≤3 mm	No	No
T1b		Yes	No
T1c		No	Yes; ≤5 mm in diameter
T1d		Yes	Yes; ≤5 mm in diameter
T2		Yes or no	Yes or no
T2a	Tumor base <9 mm with thickness 6–9 mm Tumor base 9.1–12 mm with thickness 3.1–9 mm Tumor base 12.1–15 mm with thickness ≤6 mm Tumor base 15.1–18 mm with thickness ≤3 mm	No	No
T2b		Yes	No
T2c		No	Yes; ≤5 mm in diameter
T2d		Yes	Yes; ≤5 mm in diameter
T3		Yes or no	Yes or no
T3a	Tumor base 3.1–9 mm with thickness 9.1–12 mm Tumor base 9.1–12 mm with thickness 9.1–15 mm Tumor base 12.1–15 mm with thickness 6.1–15 mm Tumor base 15.1–18 mm with thickness 3.1–12 mm	No	No
T3b		Yes	No
T3c		No	Yes; ≤5 mm in diameter
T3d		Yes	Yes; ≤5 mm in diameter
T4		Yes or no	Yes or no
T4a	Tumor base 12.1–15 mm with thickness >15 mm Tumor base 15.1–18 mm with thickness >12 mm Tumor base >18 mm with any thickness	No	No
T4b		Yes	No
T4c		No	Yes; ≤5 mm in diameter
T4d		Yes	Yes; ≤5 mm in diameter
T4e	Any tumor size	Yes or no	Yes; >5 mm in diameter

[a]Source: Edge *et al*.[51]

at or before the arterial phase, increases in intensity well into the recirculation phase, and persists for at least 45 min (86%).[63] The tumors that have broken through Bruch's membrane characteristically reveal 'double circulation' pattern (61%) because of superimposition of the intravascular fluorescence of the intact retinal vasculature over the fluorescence of large caliber vessels within choroidal tumor.[64] ICG angiography allows better visualization of intrinsic vasculature in choroidal melanoma (66%) with maximal fluorescence at an average of 18 min from injection and helps differentiate choroidal melanoma from choroidal hemangioma.[65] With computed tomography, the posterior uveal melanoma is hyperdense with slight to moderate contrast enhancement.[45] With magnetic resonance imaging, the lesion appears hyperintense on T1 and hypointense on T2-weighted image.[45]

Differential diagnosis

Differential diagnosis is an important consideration, because a variety of lesions can simulate posterior uveal melanoma. In a review of 12 000 patients referred to an oncology practice as posterior uveal melanoma, 1739 (14%) were found to have a simulating condition.[66] The most common differential diagnoses include choroidal nevus (49%), peripheral exudative hemorrhagic chorioretinopathy (8%), congenital hypertrophy of the retinal pigment epithelium (6%), hemorrhagic detachment of the retina or pigment epithelium (5%), circumscribed choroidal hemangioma (5%), and age-related macular degeneration (4%).[66]

Treatment

Following the previous discussion of the various types of melanoma, incidence and diagnosis, treatment is a crucial component for consideration. Management of posterior uveal melanoma depends on tumor location, tumor extent, tumor size, visual acuity on presentation, and systemic status.[45] Treatment options include transpupillary thermotherapy (TTT) for small choroidal melanomas, photodynamic therapy (PDT) for small amelanotic choroidal melanomas, plaque radiotherapy and proton beam radiotherapy for small and medium ciliary body (Figure 2) or choroidal melanomas (Figure 3), enucleation for large posterior uveal melanomas with poor vision at presentation, and orbital exenteration for tumors with orbital tumor extension.[45] For terminally ill patients with systemic metastasis, observation is preferred. Newer treatments on the horizon for the treatment of uveal melanoma include light-activated targeted therapy using viral-like nanoparticles administered by intravitreal injection for the early-stage treatment of primary uveal melanoma cells. This methodology is currently under scientific investigation.[67] Different types of treatment are described below in more detail.

Observation

Treatment of small posterior uveal melanoma may include observation with watchful waiting. This means that the physician would carefully monitor a patient's condition but not give treatment unless symptoms appear or change. This may be an appropriate avenue for patients whose tumors are small and stable or growing slowly. The physician would carefully balance the risks of treatment against the possible benefits.

Transpupillary thermotherapy

TTT is a noninvasive treatment modality where infrared diode 810 nm laser light is delivered through a dilated pupil to the choroidal tumor surface.[68] This increases tumor temperature to 45–60° causing obliteration of tumor-related malformed blood vessels and consequent tumor necrosis.[68] However, the depth of maximum penetration of TTT is 4 mm, thus being useful only for small choroidal melanomas.[68] The absorption of diode laser is best with more pigmented tumors.

The advantages of TTT include precise targeting of the laser, immediate tumor necrosis, ability to treat patients on an outpatient basis, and less damage to surrounding normal choroid compared with plaque radiotherapy. Complications include retinal traction (44%), branch retinal vein occlusion (26–41%), branch retinal artery occlusion (12%), cystoid macular edema (9–23%), macular epiretinal membrane (23%), vitreous hemorrhage (10%), retinal neovascularization (6%), foveal traction (4%), chorioretinal scar at fovea (4%), tractional retinal detachment (2%), optic disc atrophy (2%), rhegmatogenous retinal detachment (1%), and transient serous retinal detachment (1%), optic disc edema (<1%), and cataract (<1%).[68,69]

Tumor recurrence following TTT for choroidal melanoma is 9–28% of cases.[68,69] A direct correlation is found between tumor recurrence and the number of risk factors predictive of tumor growth (TFSOM UHHD).[69] The percentage recurrence at 10 years by Kaplan–Meier estimate was 18% with 1 or 2 risk factors, 35% with 3 to 5 risk factors, and 55% with >6 risk factors.[69] Thus, TTT is less preferable in cases with multiple risk factors.

Photodynamic thermotherapy

PDT is a minimally invasive treatment modality. A photosensitizer is administered via intravenous injection,

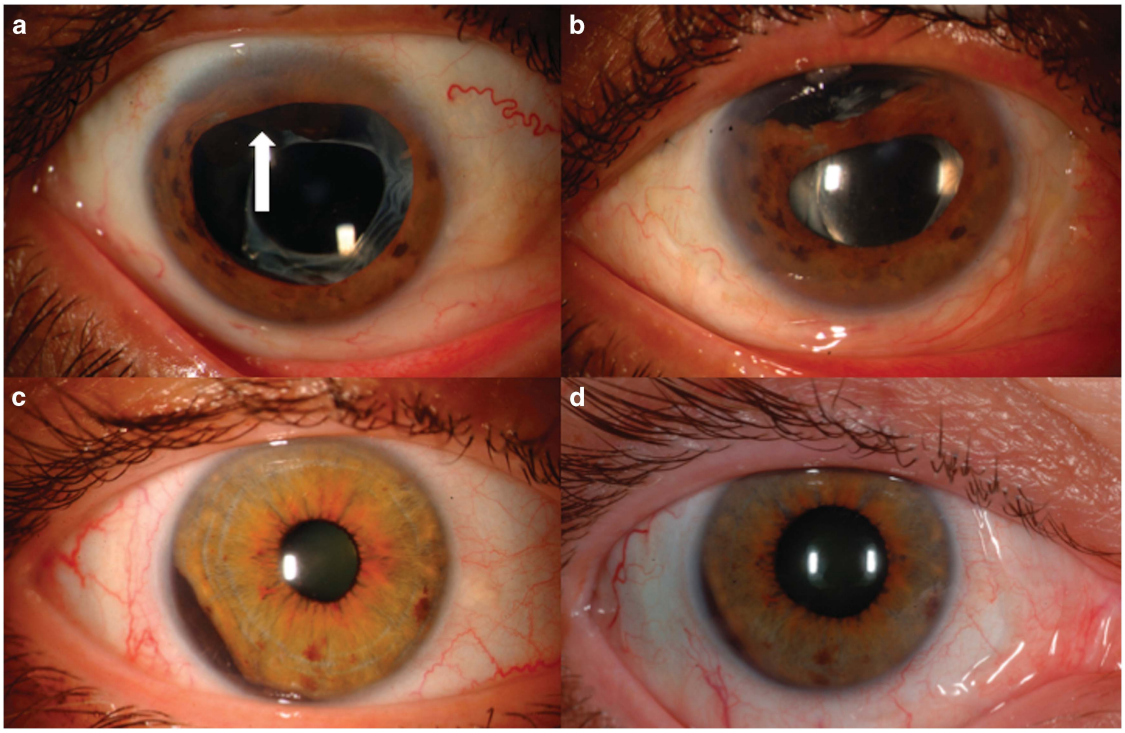

Figure 2 Ciliary body melanoma. (a) Ciliary body melanoma (white arrow) with minor extension into iris and (b) treated by partial lamellar scleroiridocyclectomy. (c) Ciliary body melanoma with extension into the iris root and (d) showed tumor control with iodine-125 plaque radiotherapy.

which accumulates in tumor tissue and when activated with light at a specific wavelength causes tumor destruction by direct cytotoxic effect, causes destruction of peritumoral vasculature, and creates local inflammatory reaction resulting in increased autophagy.[70] Verteporfin 6 mg/m^2 is the most commonly used photosensitizer. Ten minutes after intravenous injection of verteporfin, 690 nm diode laser is delivered through a dilated pupil to the choroidal tumor surface. Standard PDT treatments begin after 15 min with 600 mW/cm^2 for 83 s, which reaches a total energy of 50 J/cm^2. Some physicians use double fluence (100 J/cm^2) and double duration (166 s) of standard PDT.[70]

In a review of six reports with a total of 38 patients with choroidal melanoma in whom PDT with verteporfin was used as the primary treatment, tumor control was achieved in 80% cases and recurrence was noted in eight cases over 31 months.[70] In a review of 64 patients in whom PDT with ICG was used as the primary treatment for choroidal melanoma, tumor regression was noted in 98% of cases.[70] However, PDT is most beneficial in amelanotic melanomas with tumor thickness <4 mm.[70] No serious complications have been reported with PDT.

Radiotherapy

Plaque radiotherapy with an apex dose of 80–100 Gy is one of the most commonly used treatment modalities for posterior uveal melanoma. It is considered when the melanoma is ≤ 18 mm in diameter and ≤ 12 mm in thickness. Randomized, multicenter clinical trials conducted by the Collaborative Ocular Melanoma Study (COMS) group showed no difference in long-term survival rates of patients treated with plaque radiotherapy or enucleation in medium-sized tumors (basal diameter <16 mm and apical height 2.5–10 mm).[71] Another study showed that there was no mortality benefit with pre-enucleation radiotherapy for large tumors (basal diameter ≥ 16 mm and apical height ≥ 2 mm or any basal diameter with apical height ≥ 10 mm).[72]

Iodine-125 is the most common radioisotope used to treat posterior uveal melanoma. Ruthenium-106 and Palladium-103 are also used. When plaque radiotherapy is combined with TTT, local tumor control rates are excellent with only 3% tumor recurrence.[73] Ocular complications following iodine-125 plaque radiotherapy include radiation-induced dry eye in 8%, diplopia in 10%, strabismus in 2%, keratitis in 4–21%,

iris neovascularization in 4–23%, neovascular glaucoma in 2–45%, cataract in 8–68%, vitreous hemorrhage in 4–18%, radiation retinopathy in 10–63% radiation maculopathy in 13–52%, optic neuropathy in 4–46%, and scleral necrosis in 7–33%.[74,75]

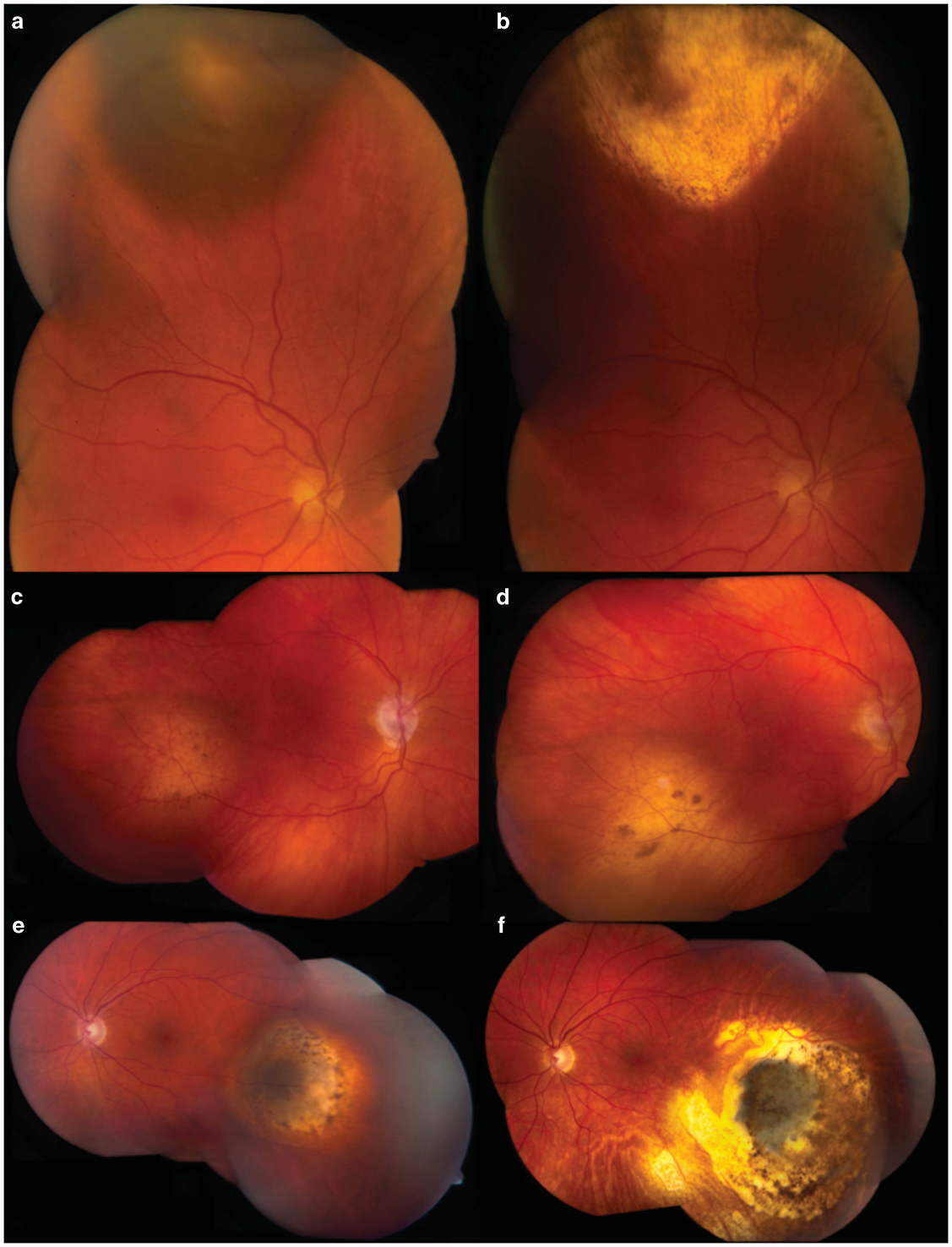

Figure 3 Management of choroidal melanoma. (a) Pigmented choroidal melanoma in the equatorial region of the right eye. (b) Flat scar following treatment with three sessions of TTT. (c) Amelanotic choroidal melanoma in the perifoveal region of the right eye and (d) completely regressed with two sessions of PDT. (e) Mixed pigmented-nonpigmented choroidal melanoma in the equatorial region of the left eye and (f) showed complete regression with iodine-125 plaque radiotherapy.

Proton beam radiotherapy is another form of radiation treatment used for posterior uveal melanoma and is comparable to plaque radiotherapy for tumor control, visual outcome, and systemic prognosis.[76] Stereotactic photon beam radiation therapy using cyber knife, gamma knife or linear accelerator can also used in the management of choroidal melanoma. The local tumor control, visual outcome, and survival of patients undergoing stereotactic photon beam radiation therapy are equivalent to those undergoing proton beam radiotherapy.[77]

Local resection

The tumor can be removed either by exoresection by *en bloc* tumor removal through a scleral opening or by endoresection in which the tumor is removed in a piecemeal manner with a vitreous cutter passed through the retina. In a review of 344 eyewall resections (exoresection) by Damato *et al*,[78] the 8-year actuarial rates of globe salvage, vision salvage of counting fingers or better, and local tumor control in eyes with no risk factors were 81%, 64%, and 75%, respectively.[78] Endoresection of choroidal melanoma is controversial because of concerns about iatrogenic tumor dissemination. A study of the long-term outcome of primary endoresection of choroidal melanoma in 71 patients revealed high rates of local tumor control with tumor recurrence in 3% patients at a median follow-up of 4 years.[79] Some surgeons use primary proton beam radiotherapy before endoresection[79] and some use adjunctive plaque radiotherapy after local resection of tumors.[78]

Enucleation

Enucleation is the second most commonly performed procedure for treating uveal melanoma. Tumors >18 mm in basal diameter and >12 mm in thickness, those with poor visual potential, and with moderate extraocular extension are advised enucleation.[45,80] The Zimmerman hypothesis indicating that enucleation of eyes with uveal melanoma accelerates the dissemination of tumor cells has been reviewed and shown to be inaccurate.[81]

Orbital exenteration

Orbital exenteration is performed in eyes with large areas of extraocular extension or those with orbital tumor extension. Eyelid sparing techniques of orbital exenteration is used in these cases.

Newer methods on the horizon

There are no currently approved targeted therapies for the treatment of early-stage ocular melanoma. One treatment currently in preclinical development is light-activated AU-011, a novel virus like particle drug conjugate as a targeted therapy for the treatment of primary uveal melanoma. The drug is administered through intravitreal injection and activation by laser to produce targeted, rapid, tumor necrosis while sparing healthy ocular tissue.[82]

Promoting tumor cell death and preserving healthy cells and tissues are the twin, often conflicting, goals of cancer treatments. The key value of the mechanism of action of AU-011 relies on the combined principles of targeted cancer therapy and multivalency. The viral particle component of AU-011 offers a multivalent tumor binding capacity over traditional bivalent antibody treatments.[82] The targeted delivery makes tumor tissue more susceptible to the cytotoxic effect of the light-activated dye component of the drug. Once the treated tumor is exposed to light at 689 nm, excitation of the dye at the site of the tumor cell membrane leads to necrotic cell death without harming other ocular structures.[83] Immunotherapy against uveal melanoma is also being studied with attempts to develop vaccine against uveal melanoma using autologous dendritic cells laden with tumor RNA.[84]

Prognosis of posterior uveal melanoma

Posterior uveal melanoma has a high tendency to metastasize and is associated with high mortality rates. The common sites of metastasis include liver (89%), lung (29%), bone (17%), skin and subcutaneous tissue (12%), and lymph node (11%).[85] In a study of long-term prognosis of patients with uveal melanoma who were observed for a median of 28 years, the Kaplan–Meier estimates of metastasis were 32% by 5 years, 50% by 15 years, 56% by 25 years, and 62% by 35 years.[86] Of those patients who died of uveal melanoma, 90% died within 15 years and 98% died within 25 years.[86] Metastasis and death beyond 25 years of diagnosis of posterior uveal melanoma is rare. The clinical, histopathologic, and cytogenetic features of uveal melanoma indicating poor prognosis with increased risk of developing metastasis[87] are listed in Table 6.

Clinical features predicting prognosis

Although the influence of age on the prognosis of uveal melanoma is uncertain, recent studies indicate that a poor prognosis is more likely associated with increasing age. Lower metastatic rates in younger patients could be

Table 6 Features predictive of poor prognosis for posterior uveal melanoma

Clinical features
Older age at presentation
Male gender
Larger tumor basal diameter
Increased tumor thickness
Ciliary body tumor location
Diffuse tumor configuration
Association with ocular/oculodermal melanocytosis
Extraocular tumor extension at presentation
Advanced AJCC category and staging
Histopathologic features
Epithelioid cytology on histopathology
High mitotic activity/PC-10/Ki-67
High values of mean diameter of 10 largest nucleoli
High microvascular density
Microvascular loops and patterns
Tumor-infiltrating lymphocytes
Tumor-infiltrating macrophages
High expression of insulin-like growth factor 1 receptor
High expression of HLA class I and II
Cytogenetic features
Chromosome 3-loss (monosomy 3)
Chromosome 8q-gain or 8p-loss
Chromosome 1p-loss
Chromosome 6q-loss
Transcriptomic feature
Gene expression profile class 2

related to smaller tumors, more robust immune response, or fewer genetic mutational events within the melanoma compared with older adults.[10,56] At 10 years, metastasis in patients aged 11–20 years is estimated at 10%, for 41–50 years is 21%, and for 71–80 years is 30%.[88] The COMS study showed no difference in uveal melanoma-related metastasis and death based on gender. However, some reports suggest a better prognosis in females compared with males, with a twofold higher rate of mortality in males compared with females in the first 10 years of posterior uveal melanoma diagnosis.[89] Hormonal factors, especially estrogen, may cause direct or indirect inhibition of development of metastasis in females.

Tumor size (largest basal diameter and thickness) is one of the most important factors predictive of metastasis and death in patients with uveal melanoma. In a meta-analysis of published reports by Diener-West *et al*,[90] the estimated 5-year mortality rates of uveal melanoma was 16% for small tumors (<2 or 3 mm tumor thickness and <10 or 11 mm basal diameter), 32% for medium tumors (3–8 mm tumor thickness and <15 or 16 mm basal diameter), and 53% for large tumors (>8 mm tumor thickness and >15 mm basal diameter). In a study of 8033 consecutive uveal melanoma patients at a single center with precise data collection, each millimeter increase in tumor thickness was associated with ~5% increased risk for metastasis at 10 years.[2] Kaplan–Meier estimates of metastasis at 10 years was 12% for small melanoma (≤3 mm tumor thickness), 26% for medium melanoma (3.1–8 mm), and 49% for large melanoma (>8 mm).[2]

Melanomas arising from or within the ciliary body are more aggressive compared with iris or choroid melanoma. This may be related to the delayed detection of these large tumors, rich blood supply of the ciliary body that increases the risk of hematogenous spread, predilection for monosomy 3 and 8q-gain, and tumor microvascular patterns.[87] A significant relationship exists between the anatomic site and melanoma-related metastasis, with two to four times higher chance of metastasis in a ciliary body melanoma compared with choroidal melanoma.[91] The other clinical features with increased melanoma-related metastatic rate include diffuse growth pattern, associated ocular/oculodermal melanocytosis, and extraocular extension.

AJCC classification is an important prognostic factor of posterior uveal melanoma. In a study of 7731 patients with posterior uveal melanoma based on T category of AJCC classification, the risk for metastasis and death increased twofold with each increasing tumor category, and the 10-year metastatic rate was 15% for T1, 25% for T2, 49% for T3, and 63% for T4 tumors.[92]

Histopathology features predicting prognosis

The histopathologic features predicting poor prognosis of uveal melanoma include epithelioid cell type, high mitotic activity, large mean diameter of the 10 largest nucleoli, high microvascular density, presence of microvascular loops and networks, increased tumor-infiltrating lymphocytes and macrophages, and higher expression of insulin-like growth factor 1 receptor, and HLA class I and II antigens.[87] Currently, most authorities rely on cytogenetic features rather than histopathologic features for prognostication.

Cytogenetic features

Aberrations in chromosomes 1, 3, 6, and 8 determine the survival in patients with uveal melanoma. The presence of monosomy 3 indicates high-risk melanoma, with an increased risk for metastasis.[93] Monosomy 3 is associated with higher incidence of clinical and histopathologic risk factors including larger tumor diameter, ciliary body tumor location, extraocular extension, epithelioid cell type, high mitotic rate, and increased vascular loops. The 3-year mortality rate in patients with tumors with monosomy 3 is 50%, and for those with no monosomy 3 is 0%.[93] BAP1 has been mapped on chromosome 3p21.1,

and identification of BAP1 mutation has strong prognostic value.[37,38]

Chromosome 8q-gain most commonly coexists with monosomy 3 and is more closely associated with poor prognosis than with 8q-gain alone or monosomy 3 alone. Concomitant loss of chromosomes 1p and 3 has a stronger correlation with melanoma-related metastasis than either one separately.[87] Chromosome 6p gain is usually mutually exclusive with monosomy 3 and is a strong indicator of good prognosis of uveal melanoma, whereas 6q loss is associated with poor prognosis.[87]

In a study of 500 cases of uveal melanoma, disomy 3 was found in 48%, partial monosomy in 27%, and complete monosomy 3 in 25% cases. The 3-year cumulative probability of metastasis was 3% for disomy 3, 5% for partial monosomy 3, and 24% for complete monosomy 3.[94] A multivariate analysis of the joint effects of changes in the six chromosomal regions in 320 uveal melanoma cases revealed increased risk of metastasis with chromosome 3-loss, 1p-loss, 8p-loss, and/or 8q-gain with hazard ratios ranging from 7.90 to 37.25.[95] Tumors with chromosome 3 disomy/BAP1-WT/EIF1AX-WT have a 10-fold increased risk of metastasis compared with disomy 3/BAP1-WT/EIF1AX mutant tumors.[96]

Transcriptomic features

Gene expression profiling (GEP) of tumor biopsies may also be used to predict prognosis.[97] Two classes of uveal melanoma, class 1 and 2 were identified on mRNA analysis by GEP.[97] Most class 1 tumors are associated with disomy 3, and chromosome 6p gain and are considered low-risk tumors. Most, if not all class 2 tumors, however, have monosomy 3 and are considered high-risk tumors with a greater rate of metastasis and melanoma-related mortality.[97] In a study of 459 patients with uveal melanoma from 12 oncology centers, a strong association was noted between GEP and prognosis of uveal melanoma, with 1% metastasis in class 1 cases and 26% metastasis in class 2 cases at a median follow-up of 17 months.[98] Patients with class 2 tumors tended to be older, and have increased tumor thickness, epithelioid cells, high mitotic rate, and mutations in the BAP1 tumor suppressor gene. For this reason, genetic testing is becoming an important component in diagnosing uveal melanoma and determining prognosis.

The importance of early detection and treatment

The aforementioned therapies regularly achieve good local disease control. The earlier a melanoma is detected the better the prognosis.[99] Any pigmented choroidal lesion suspicious of small choroidal melanoma should be assessed for thickness (>2 mm), subretinal fluid, symptoms (decreased vision, visual field defect, flashes, floaters), orange pigment, margin ≤3 mm from the optic disc, ultrasonographic hollowness, and absence of halo or drusen (TFSOM UHHD)[35,36] (Figure 4). Choroidal nevus with any of the one factor of TFSOM UHHD have a 38% chance and those with two or more factors have over 50% chance for transformation into melanoma at 5 years.[35,36] The most dangerous combination of factors with 69% risk for growth include thickness >2 mm, symptoms, and tumor margin near the disc.[35,36] An asymptomatic choroidal nevus with thickness <2 mm displaying signs of chronicity such as drusen, RPE atrophy, RPE hyperplasia, RPE detachment, and RPE fibrous metaplasia, with/without surrounding halo, and with no overlying orange pigment or subretinal fluid is considered as a 'low-risk choroidal nevus' with minimal chance of transformation into melanoma. A choroidal nevus with one or more risk factors (greater thickness (>2 mm), subretinal fluid, symptoms, orange pigment, margin near disc, ultrasonographic hollowness, and absence of halo or drusen) is a 'high-risk choroidal nevus' with a greater chance of transformation into melanoma. Those tumors with two or more risk factors probably represent small choroidal melanoma and early treatment is indicated.[35,36]

The most important clinical predictor of metastasis remains cytogenetics and tumor size.[2,94–98] With an assumption of constant growth rate of metastases, Eskelin *et al*[100] estimated that micrometastases from uveal melanoma could develop as early as 5 years before the treatment of the primary tumor. At this estimated time of micrometastases, the theoretically estimated size of the primary tumor would be ~3 mm in diameter and 1.5 mm in height or only 7 mm^3 in volume.[100] This underscores the importance of early diagnosis of uveal melanoma and possible benefit of adjuvant systemic chemotherapy in patients with uveal melanoma at the time of initial diagnosis. As in many other cancer indications, both early detection and early treatment (Figure 4) may be critical for a positive long-term survival outcome in uveal melanoma. Taken together, these observations call attention to an unmet medical need for the early treatment of small melanocytic lesions or small melanomas in the eye to achieve local disease control and vision preservation.

The combination of early detection, gene expression profiling, and vision-sparing treatments have the potential to help patients earlier in the treatment process before their tumors are capable of metastasis. More research in these areas could provide a great benefit for patients in the near future.

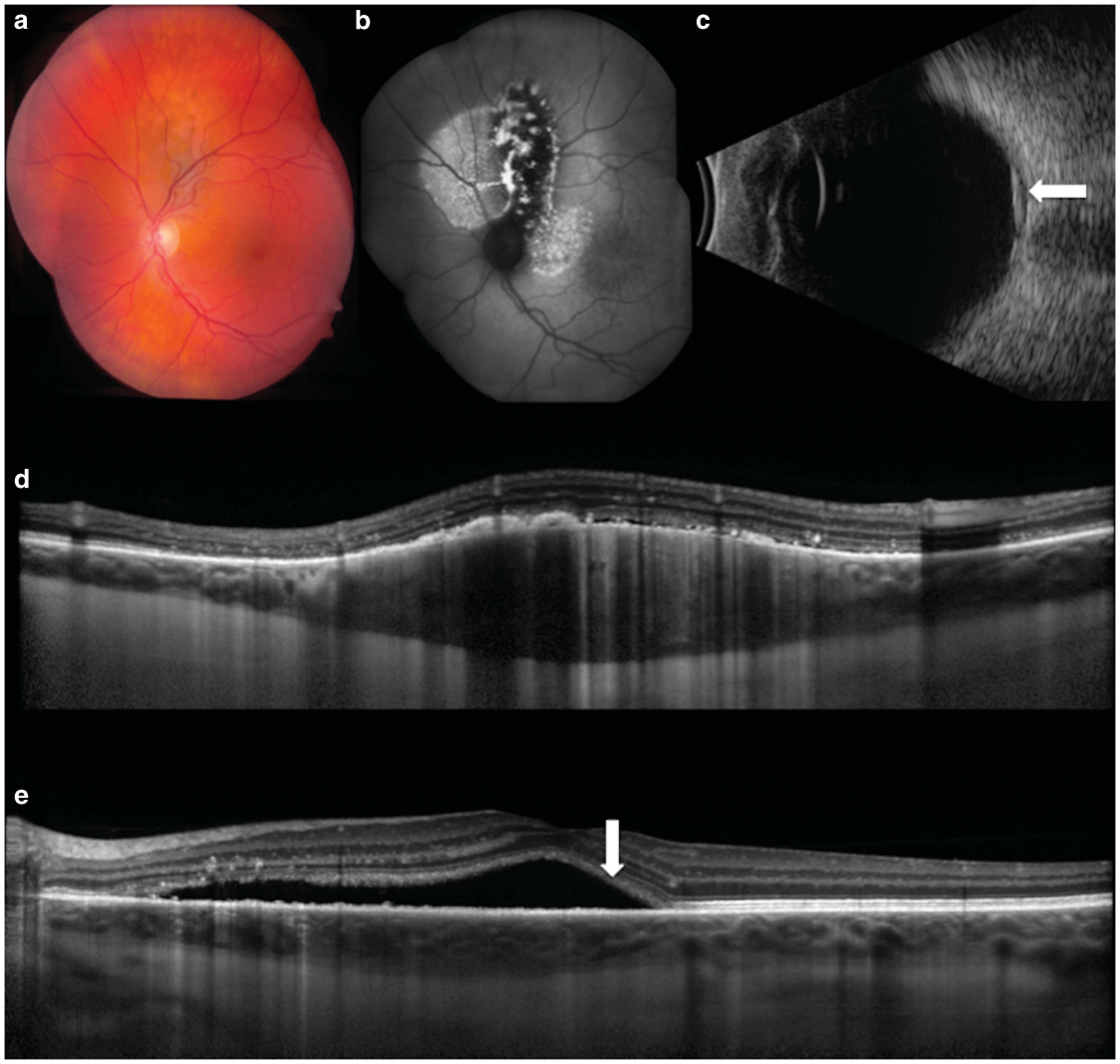

Figure 4 Small choroidal melanoma with all eight risk factors TFSOM UHHD (tumor thickness >2 mm, subretinal fluid, symptoms, orange pigment, margin near disc, ultrasonographic hollowness, and absence of halo or drusen). (a) Fundus photograph showing peripapillary small choroidal melanoma above the optic disc. (b) Fundus autofluorescence demonstrating bright hyperautofluorescence due to lipofuscin pigment within the tumor and surrounding hyperautofluorescence due to subretinal fluid. (c) B-scan USG showing a 2.3-mm-thick choroidal lesion with acoustic hollowing and choroidal excavation (white arrow). (d) EDI-OCT showing choroidal thickening with compression of overlying choriocapillaries. (e) EDI-OCT showing subretinal fluid and shaggy photoreceptors (white arrow) in the fovea and perifoveal region.

Conclusion

This review of ocular melanoma provides comprehensive analyses including risk factors, diagnosis, and treatment (existing and newer methods) of this rare and important disease, uveal melanoma. With moderately high mortality rates, there is clearly an unmet need for these patients, and newer treatments should be explored to control melanoma before it demonstrates capacity to spread. Early detection using published risk factors[35,36] and established or newer treatments, especially with targeted therapy at an earlier point in tumor development, could offer greater patient benefit.

Conflict of interest

The authors declare no conflict of interest.

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