Chapter

Ocular Melanoma

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Abstract

Ocular melanoma is the most common malignant tumor in adults after cutaneous melanoma. There is a wide clinical spectrum depending upon the location of the tumor. The various predispositions, risk factors, tumor classification, and treatment modalities are discussed. Choroidal melanoma is the most common type of ocular melanoma. Its management has evolved over the years. The Collaborative Ocular Melanoma Study (COMS) has helped to precisely classify choroidal melanoma and standardize its treatment. The future lies in the genetics which can help prognosticate and provide adjuvant treatment to patients at risk.

Keywords: melanoma, plaque brachytherapy, coms

1. Introduction

The incidence of melanoma continues to rise globally with significant mortality in spite of modern treatment protocols [1]. Ocular melanoma is the most common type of melanoma in adults after the cutaneous melanoma. It constitutes 3.7% of all melanomas [2]. It results due to the abnormal proliferation of the melanocytes in the eye. Based on the location, the ocular melanoma can be broadly classified as follows:

1. Eyelid melanoma
2. Conjunctival melanoma
3. Uveal melanoma
    a. Iris melanoma
    b. Trabecular meshwork melanoma
    c. Iridotrabeculociliary or iridociliary melanoma
    d. Ciliary body melanoma
    e. Choroidal melanoma
    f. Ciliochoroidal melanoma

2. Eyelid melanoma

Eyelid melanoma is relatively and comprises less than 1% of all eyelid cancers. Serial documentation and close monitoring of suspicious lesions play a very important role in early diagnosis. Variable pigmentation, rapid increase in size, change in color, abnormal vascularity, and tendency to bleed are the typical features of eyelid melanoma [3].

3. Conjunctival melanoma

3.1 Epidemiology

The clinical spectrum of melanocytic tumors of the conjunctiva constitutes about 53% of all conjunctival tumors. The reported incidence is two cases per million per year, but the incidence is increasing. It usually occurs at a median age of 62 years and is very rare in children [4, 5].

3.2 Risk factors

1. PAM: 22% (overall: 9%, with atypia: 13%, and without atypia: 0%)

2. Preexisting nevus in 15%

3. De novo 5% [6, 7]

4. Dysplastic nevus syndrome

5. Neurofibromatosis

6. Xeroderma pigmentosum [8]

3.3 Clinical presentation

1. Fleshy, variably pigmented (tan to dark brown) placoid, or modular elevated lesion located on the limbal, bulbar, forniceal, or palpebral conjunctiva. The lesions which are localized, bulbar, thin, and limbal have a good prognosis where as those which are large, diffuse, forniceal, on caruncle and tarsus have poorer prognosis (**Figure 1**).

2. Prominent feeder vessels (conjunctival and scleral)

3. It can develop secondarily in contiguity with an eyelid margin which is called as implantation melanoma [9].

3.4 Treatment

1. A careful dissection of the mass with "no-touch technique," wide excision with frozen section margin control is ideal.

2. Alcohol keratoepitheliectomy for the corneal involvement.

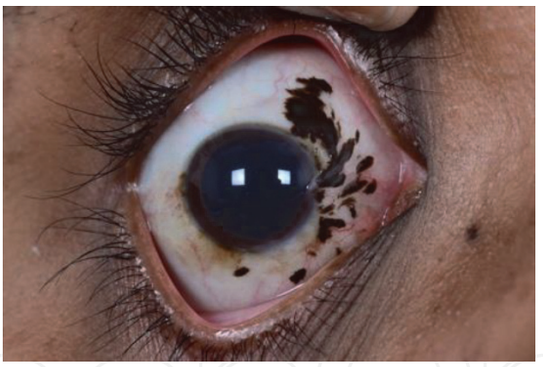

Figure 1.
Conjunctival melanoma.

3. Double freeze thaw cryotherapy of the resection edge and the clinically suspected involved base if it is less than 3 clock hours.

4. Episcleral plaque brachytherapy if base is involved for more than 3 clock hours. Plaque rotation can be customized depending on the tumor extent.

5. Interferon and interleukin-2 in combination can be administered in disseminated melanoma [8].

6. Sentinel lymphangiography is indicated in tumors more than 2 mm and helps in complete removal of the lymph nodes.

3.5 Histopathology

Abnormal proliferation of the melanocytes, spindle, or the epitheloid cells.

3.6 Prognosis

1. Metastasis to ipsilateral facial lymph nodes, brain, lung, skin, bone, and liver are the most common.

2. Multiple recurrences, especially those within the orbit, might require orbital exenteration [4].

3. Intraocular and intraorbital involvement may require modified enucleation and orbital exenteration, respectively.

4. Recurrences after the therapy are 50–70% at 10 years.

5. Overall mortality rate is 25% at 10 years and more than 30% in 15 years [9, 10].

6. The 10 year rate of metastasis is PAM 25%, Nevus 26%, De novo 49% [11]

7. The prognosis can be predicted by the AJCC-TNM staging of conjunctival melanoma (**Table 1**).

8. The factors predictive of metastasis or death are de novo origin, tarsal or forniceal location, nodular mass, and orbital invasion [11].

3.7 Newer innovations

Definition of primary clinical tumor (cT)
TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
T1 Tumor of the bulbar conjunctiva
T1a < 1 quadrant
T1b > 1 but <2 quadrants
T1c > 2 but <3 quadrants
T2 Tumor of nonbulbar conjunctiva (forniceal, palpebral, tarsal, caruncle)
T2a Noncaruncular and < 1 quadrant nonbulbar conjunctiva
T2b Noncaruncular and > 1 quadrant nonbulbar conjunctiva
T2c Caruncular and < 1 quadrant nonbulbar conjunctiva
T2d Caruncular and > 1 quadrant nonbulbar conjunctiva
T3 Tumor of any size with local invasion
T3a Globe
T3b Eyelid
T3c Orbit
T3d Nasolacrimal duct and/or lacrimal sac and/or paranasal sinuses
T4 Tumor of any size with invasion of central nervous system.
Definition of regional lymph nodes (N)
NX Regional lymph nodes cannot be assessed
N0 Regional lymph node metastasis absent
N1 Regional lymph node metastasis present
Definition of distant metastasis (M)
M0 Distant metastasis absent
M1 Distant metastasis present
Definition of primary pathological tumor (pT)
TX Primary tumor cannot be assessed
T0 No evidence or primary tumor
Tis Tumor confined to conjunctival epithelium
T1 Tumor of bulbar conjunctiva
T1a Tumor with <2 mm thickness invasion of substantia propria
T1b Tumor with >2 mm thickness invasion of substantia propria
T2 Tumor of nonbulbar conjunctiva
T2a Tumor with <2 mm thickness invasion of substantia propria
T2b Tumor with >2 mm thickness invasion of substantia propria
T3 Tumor of any size with local invasion
T3a Globe
T3b Eyelid
T3c Orbit
T3d Nasolacrimal duct and/or lacrimal sac and/or paranasal sinuses
T4 Tumor of any size with invasion of central nervous system

Table 1.
AJCC 8th edition classification of conjunctival melanoma.

1. Pembrolizumab—for recurrent conjunctival tumors [12]

2. Nivolumab [13]

4. Uveal melanoma

It is the most common primary intraocular malignancy in adults. The earlier detection and prompt treatment has decreased the morbidity to some extent over the years.

Based on the location, they can be classified into

a. Iris melanoma

b. Trabecular meshwork melanoma

c. Iridotrabeculociliary or iridociliary melanoma

d. Ciliary body melanoma

e. Choroidal melanoma

f. Ciliochoroidal melanoma

The most common differential diagnosis of uveal melanoma is anevus. The following are the key points to differentiate the two (pneumonic: ABCDEF):

1. Age ≤ 40 years

2. Blood vessels

3. Clock hours inferiorly

4. Diffuse configuration

5. Ectropion uveae

6. Feathery margin

4.1 Iris melanoma

4.1.1 Epidemiology

Iris melanoma constitutes about 4% of uveal melanomas [14]. The mean age at presentation is 40–47 years. It is very rarely seen in the pediatric age group. Males and females are equally affected. It is most commonly seen in Caucasians (97.8%) [15].

4.1.2 Clinical presentation

Nodular pigmented lesion usually seen in the inferior iris. It is usually associated with tumor seeding in the adjacent iris or trabecular meshwork and secondary glaucoma.

4.1.3 Types

1. Circumscribed

2. Diffuse

4.1.4 Management

1. Observation of clinically suspicious lesions

2. Local resection (iridectomy/iridocyclectomy) for tumors less than 3–4 clock hours

3. Plaque brachytherapy—has up to 87% chance if tumor control after local resection

4. Proton beam therapy

5. Enucleation—for diffuse, recurrent tumors or eyes with intractable glaucoma

4.1.5 Differential diagnosis

1. Primary iris cyst

2. Iris nevus

3. Essential iris atrophy

4. Iris foreign body

5. Peripheral anterior synechiae

6. Iris metastasis

4.1.6 Factors predictive of metastasis

1. Increased age at diagnosis [16, 17]

2. Angle invasion

3. Elevated intraocular pressure

4. Extraocular extension

5. Previous surgical intervention before referral prognosis [14]

Prognosis is better than ciliary body or choroidal melanoma with a 10-year metastasis of 7% as compared to 25% in choroidal melanoma and 34% for ciliary body melanoma.

4.2 Ciliary body melanoma

It is relatively a rare uveal tumor and is reported in one of 10 cases of all intraocular melanomas [18, 19].

4.2.1 Clinical presentation

1. Diminution of vision due to astigmatism or lens dislocation

2. Painless visual field loss or pain due to acute glaucoma

3. Episcleral sentinel vessels

4. Unexplained relatively low intraocular pressure

Management options include local resection, plaque brachytherapy, proton beam radiation, and enucleation.

4.2.2 Histopathological types (callender classification)

1. Spindle A and B type melanoma—best prognosis

2. Mixed cell melanoma

3. Epitheloid cell melanoma—poor prognosis

4. Necrotic melanoma—poor prognosis

4.2.3 Metastasis

Hematogenous metastasis is faster in ciliary body melanoma as a result of continuous contractions of the ciliary muscle and rich vascularization.

T Category and criteria
T1—Tumor limited to the iris T1a—Tumor limited to the iris, not more than 3 clock hours in size T1b—Tumor limited to the iris, more than 3 clock hours in size T1c—Tumor limited to the iris with secondary glaucoma T2—Tumor confluent with or extending into the ciliary body, choroid, or both T2a—Tumor confluent with or extending into the ciliary body, without secondary glaucoma T2b—Tumor confluent with or extending into the ciliary body and choroid, without secondary glaucoma T2c—Tumor confluent with or extending into the ciliary body, choroid, or both with secondary glaucoma
T3—Tumor confluent with or extending into the ciliary body, choroid, or both, with scleral extension
T4—Tumor with extrascleral extension T4a—Tumor with extrascleral extension ≤5 mm in largest diameter T4b—Tumor with extrascleral extension >5 mm in largest diameter
G Category and criteria
GX—Grade cannot be assessed G1—Spindle cell melanoma (>90% spindle cells) G2—Mixed cell melanoma (>10% epitheloid cells and < 90% spindle cells) G3—Epitheloid cell melanoma (>90% epitheloid cells)
N Category and criteria
N1—Regional lymph node metastasis or discrete tumor deposits in the orbit N1a—Metastasis in one or more regional lymph node(s) N1b—No regional lymph nodes are positive, but there are discrete tumor deposits in the orbit that are not contiguous to the eye
M Category and criteria
M0—No distant metastasis by clinical classification M1—Distant metastasis M1a—Largest diameter of the largest metastasis ≤3 cm M1b—Largest diameter of the largest metastasis 3.1–8 cm M1c—Largest diameter of the largest metastasis ≥8.1 cm

Table 2.
AJCC 8th edition classification of iris melanoma [20].

Clinical	Macroscopic	Microscopic
Local/general signs	Size of the tumor	Epitheloid and necrotic cellular patterns
Local extension	<11 mm—small	Necrosis
Presence of metastasis	11–15 mm—medium	Intense pigmentation
Age of the patient	>15 mm—large	Melanophagic, lymphocytic infiltrate
Dysplastic nevi		

Table 3.
The prognostic factors for ciliary body melanoma.

Host factors	Environment factors
Light colored eyes	Intermittent ultraviolet exposure to arc welding
Fair skinned	Chronic UV exposure
	Occupational sunlight exposure

Table 4.
Predisposing factors.

4.2.4 Prognosis

The prognostic factors are listed in **Table 3**.

4.3 Choroidal melanoma

Choroidal melanoma is the most common uveal melanoma and constitutes about 90% of all uveal melanomas. This is usually seen in an elderly age group at around 60 years and there is no gross gender predilection. It is seen predominantly in Caucasians (98%), as compared to other races. It has a pronounced tendency to metastasize resulting in high mortality [21]. Predisposing factors are listed in **Table 4**.

4.3.1 Clinical presentation

It can be incidentally detected in asymptomatic patients on routine ocular examination. Most of the patients, however, manifest with diminution of vision, floaters, photopsia, visual field loss, or pain due to impingement of posterior ciliary nerve or angle closure glaucoma. It can metastasize to liver (89%), lung (29%), and bone (17%). Median survival after metastasis is 6–12 months [22]. Males have a poor prognosis than females. The lower metastatic rate in females can be explained due to the inhibitory action of estrogen on the growth of micrometastases within the liver [23, 24].

4.3.2 Classification

Choroidal melanoma can be broadly classified into diffuse (**Figure 2**) and circumscribed (**Figure 3**). The circumscribed variant can either be dome-shaped (75%) or mushroom-shaped (20%). Diffuse choroidal melanoma is seen in 3–17% cases and has a substantial risk of metastasis despite its flat appearance. The poor prognostic factors include delayed diagnosis, greater proportion of epitheloid cells, and a tendency for extraocular extension [25].

AJCC Classification has already been mentioned under the section of iris melanoma (**Table 2**).

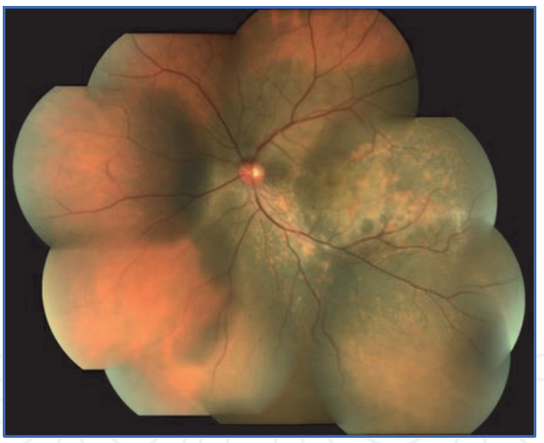

Figure 2.
Diffuse choroidal melanoma.

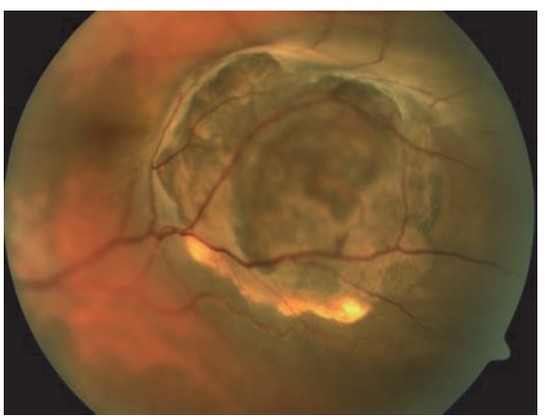

Figure 3.
Circumscribed choroidal melanoma.

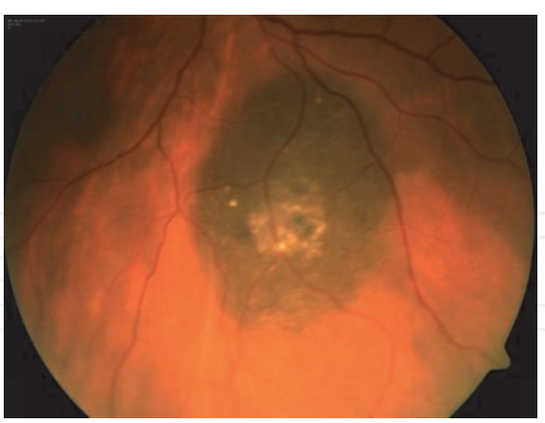

Figure 4.
Choroidal nevus.

The most common precursor lesion for choroidal melanoma is the preexisting choroidal nevus (**Figure 4**), followed by oculodermal melanocytosis.

The following are used to differentiate a choroidal nevus from a melanoma (pneumonic: to find small ocular melanoma using helpful hints daily):

1. Thickness > 2 mm

2. Fluid

3. Symptoms

4. Orange pigmentation

5. Margin <3 mm to disk

6. Ultrasound hollow

7. Absent halo

8. Absent grusen

4.3.3 Investigations

4.3.3.1. Ultrasonography

It has 95% accuracy and is useful to estimate tumor size for periodic observation and to evaluate for extraocular extension.

The characteristic features on A-scan are:

1. Initial prominent spike

2. Low to medium internal reflectivity with diminishing amplitude

3. Fine oscillation of internal spiking pattern (vascular pulsations)

The characteristic features on B-scan are:

1. Low to medium internal reflectivity

2. Choroidal excavation

3. Shadowing of subadjacent soft tissue

4. Internal vascularity

5. Acoustic hallowing

4.3.3.2. Autofloroscence

Hyperautofluorescence of orange-colored lipofuscin pigment.

4.3.3.3. Fundus fluorescein angiography

Small melanoma: Hypofluorescence (blocked fluorescence)

Large melanoma: Patchy pattern of early hypofluorescence and hyperfluorescence followed by late intense staining. Double circulation—internal vascularity

4.3.3.4. Ultrasound biomicroscopy

It helps to differentiate anterior tumors from those of ciliary body origin. Although the tumor margins and extent is well delineated by UBM, the resolution of internal tumor details is limited.

4.3.3.5. Optical coherence tomography

Dome-shaped choroidal mass with overlying outer retinal thickening and subretinal fluid.

Optical coherence tomography angiography shows reduced capillary density in the affected eye.

4.3.3.6. Magnetic resonance imaging

Pigmented melanomas can be seen as T1 Hyperdense and T2 hypodense intraocular masses.

4.3.3.7. Fine needle aspiration cytology

Although reliable, it is technically challenging and requires expertise.

4.3.4 Management

The most common treatment modality is the episceral plaque brachytherapy. Plaque brachytherapy is suitable for tumors up to 16 mm in diameter and up to 6 mm thickness with Ruthenium-106 and up to 8 mm thickness with Iodine-125. The dose to the tumor apex should be 10,000 cGy and almost up to 90% tumor control can be achieved. Enucleation is an option for tumors beyond the scope of plaque brachytherapy. Orbital exenteration might be required in tumors with orbital invasion. The proton beam irradiation has a higher chance of eye salvage but the availability and affordability are the considerable limitations. The other treatment modalities include laser photocoagulation, transpupillary thermotherapy, chemotherapy, and immunotherapy.

The various newer treatment modalities under evaluation are:

1. Chemotherapy with dacarbazine+interferon alpha, cisplatin, tamoxifen +sunitinib, and fotemustine.

2. Targeted therapy with crizotinib, sunitinib, and valproic acid.

3. Immunotherapy with Ipilimumab with nivolumab.

4.3.5 Histopathology

Modified Callenders's classification describes various patterns on histopathology.

1. Spindle cell nevi

2. Spindle cell melanoma

3. Necrotic melanoma

4. Epitheloid cell melanoma

5. Mixed cell melanoma

Clinical features	Histopathologic features	Cytogenetic features	Transcriptomic feature
Older age at presentation	Epithelioid cytology	Chromosome 3 loss (monosomy 3)	Gene expression profile class 2
Male gender	High mitotic activity/PC-10/ Ki-67	Chromosome 8q gain or 8p loss	
Larger tumor basal diameter	High values of mean diameter of 10 largest nucleoli	Chromosome 1p loss	
Thicker tumor	High microvascular density	Chromosome 6q loss	
Ciliary body tumor location	Microvascular loops and patterns	Chromosome 9q loss	
Diffuse tumor configuration	Tumor-infiltrating lymphocytes, macrophages	BAP1 loss	
Association with ocular/ oculodermal melanocytosis	Loss of nuclear immunostaining for BAP1		
Extraocular tumor extension	High expression of insulin-like growth factor 1 receptor		
Advanced AJCC category and staging	High expression of HLA class I and II		

Table 5.
The poor prognostic factors include [26].

The epitheloid cell and the mixed cell melanoma have the poorest prognosis among all the subtypes (**Table 5**). Immunohistochemical markers characteristic of choroidal melanoma are S-100, HMB-45.

4.3.6 Metastasis

The risk factors for metastasis include (**Table 7**):

1. Thickness > 2 mm

2. Symptoms

3. Margin <3 mm to disk

4. Documented growth

The presence of four risk factors has a metastatic rate of 20% but the absence of risk factors has only <1% risk of systemic metastasis. Also, each millimeter increase in thickness adds 5% risk for metastasis at 10 years and a hazard ratio of 1.08 [27]. Doubling time of untreated metastases ranged from 34 to 220 days (median, 63 days). The metastasis from tumors as small as $3 \times 3 \times 1.5$ mm has been noted in a study [28]. Based on the estimated growth rates, a rational follow-up interval to detect metastatic uveal melanoma would be 4–6 months. Primary uveal melanomas that develop clinically detectable metastasis after conservative therapy may have micrometastasized several years before treatment.

Damato's classification of metastasis [26]:

1. Metastasizing melanomas, which have already metastasized by the time of ocular treatment even though the metastases may not be detectable.

2. Pre-metastasizing melanomas, which develop metastatic capability and disseminate if treatment is delayed.

3. Non-metastasizing melanomas, which do not metastasize even if never treated.

4.3.7 Colloborative ocular melanoma study

This is the largest study ever to be performed in Ocular oncology with 43 participating centers and more than 2000 patients [29, 30].

Objectives of the study:

1. To evaluate the therapeutic interventions for patients with choroidal melanoma

2. To determine which of the two, enucleation or brachytherapy prolongs the lifetime of an individual, and if both have a similar survival, then which offers the longer cancer-free survival and better prognosis for vision.

Inclusion and exclusion criteria:

- Primary choroidal melanoma in one eye
- Less than 50% involvement of ciliary body
- Age 21 years or older
- Ability to give informed consent
- Ability to return for treatment and scheduled follow-up
- No primary cancer (except noninvasive nonmelanotic skin cancer/CIS cervix)
- No coexisting disease threatening survival (5 years or longer)
- No metastatic melanoma
- No contraindication for surgery/RT
- No previous FNAB
- No previous treatment
- No extrascleral extension of 2 mm or more
- No diffuse, ring or multifocal tumor
- No iris/angle involvement
- No use of immunosuppressive therapy that cannot be discontinued

Outcome measures:

1. Primary outcome: Time to death from all-cause mortality

2. Secondary outcome: Metastasis-free survival, cancer-free survival, and years of useful vision

Trial design and treatment groups:

1. Small <3 (1.5–2.4) mm, 5 mm (observational group)

2. Medium 3–8 (2.5–10) mm, 16 mm (randomized group)

3. Large >8 (10 mm), >16 mm (randomized group)

Results:

1. Pre-enucleation EBRT for large melanoma has no advantage over enucleation group. Five-year Kaplan–Meier estimates for survival were 57% for the enucleation group and 62% for the pre enucleation radiation group.

2. Enucleation versus brachytherapy for medium melanoma were comparable. The cumulative all-cause mortality at 12 years was 43% for patient in the plaque radiotherapy group versus 41% for those in enucleation group.

3. The small tumor trial showed that small choroidal melanomas managed by observation showed tumor growth in 21% by 2 years and 31% by 5 years. Observation for small melanoma is not acceptable now and is treated appropriately.

4.3.8 Genetic markers

The mitogen-activated protein kinase (MAPK) pathway is one of the main regulatory pathways involved in choroidal melanoma development, particularly through mutations in BRAF, NRAS, and KIT. Choroidal melanoma with BRAF mutation is common in younger patients and the ones associated with preexisting nevi. KIT mutations are the least common choroidal melanoma mutation in MAPK pathway. NRAS mutation is very rare in choroidal melanoma [21–33]. Disomy 3 and chromosome 6p gain are associated with a good prognosis.

Chromosome 3 loss, 8q gain, 1p loss and 6q loss = Class 1 associated with poor prognosis.

Based on gene expression prolifes (GEP), uveal melanoma is now classified into three prognostic categories for metastasis (**Table 6**).

The GEPs are playing a major role at present in prognosticating the risk of metastasis. The tumor as such is constantly evolving at the genetic and molecular level which is described as intratumoral genetic heterogeneity. The term cresendo malignancy is described which explains the transformation of a small tumor which is slow growing over years but acquires Class 2 genetic changes over time (**Table 6**).

		Systemic metastasis at 5 years
Class 1A	Low risk	2%
Class 1B	Intermediate risk	21%
Class 2	High risk	72%

Table 6.
Prognostic categories for metastasis.

Tumor size	Monosomy 3	If M3, metastasis by 3 years
Small 0–3 mm	23%	0%
Med 3–8 mm	35%	24%
Large >8 mm	>50%	58%

Table 7.
Metastasis depends on several factors: Size, markers-BAPI, and genetics [34].

4.3.9 Follow-up

A periodic follow-up with systemic investigations is mandatory in view of high metastatic rates of choroidal melanoma. An annual PET-CT scan is ideal, however, the monitoring of the liver function tests, ultrasonography of the abdomen and the chest X-Ray are reasonably good.

5. Conclusion

Ocular melanoma is being effectively managed currently. A protocol-based management of the patient can lead to good local tumor control and careful systemic monitoring can decrease the morbidity and mortality to a great extent. The ongoing research in genetics will probably help us understand and prognosticate ocular melanoma in a better way.

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Conflict of interest

The authors declare no conflict of interest.

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