

Diagnostic and Treatment Criteria in Malignant Choroidal melanoma (MCM)

Marieta Dumitrache*, Rodica Lascu, Manea M and Miruna Cioboata

University of Medicine and Pharmacy Bucharest, Romania.

*Correspondence:

Marieta Dumitrache, University of Medicine and Pharmacy Bucharest, Romania.

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ABSTRACT

The most common primary intraocular tumor of adults with clinical manifestations between 40-70 years of age is malignant choroidal melanoma (MCM), which represents 85% of uveal tumors, and which is frequently accompanied by serous retinal detachment. Symptomatically, MCM presents decreased vision (37%) depending on the extent, size, and location of the tumor; photopsia, visual field changes, but it can also be asymptomatic. Eye fundus examination reveals a prominent subretinal brown tumor with orange pigment on the surface, with a double vascular, tumoral and choroidal network. MCM can be complicated with retinal detachment (RD), cataract, secondary glaucoma, uveitis, vitreous hemorrhage. The reserved prognostic factors are: the presence of numerous epithelioid cells, vascular loops at the level of the tumor, associated with age greater than 65 years. In the evolution of MCM, depending on the size and extension of the tumor, the orbit may be invaded or there may be metastases in the liver, lungs, CNS, or recurrence after enucleation. MCM treatment is surgical, enucleation being indicated depending on the clinical stage, location, and tumor extension. The conservative treatment of MCM is radiotherapy (brachytherapy, with radioisotopes, I125, palladium 106, ruthenium 103, iridium 192, external radiotherapy in larger tumors and located below 4mm of the papilla and fovea, proton radiotherapy, transpupillary thermotherapy), and argon laser photocoagulation with limited indication and questionable efficiency (5% of patients benefit). Enucleation is indicated in large tumors, in eyes with low / lost vision, in invasive, extensive tumors, the surgical alternative being resection of the tumor with precise indications. Exenteration is indicated in extraocular extension of the tumor or in recurrence. Cytotoxic chemotherapy with alkylating agents (cisplatin, sunitinib) and immunotherapy. Any MCM must be diagnosed early, carefully monitored and the appropriate treatment of the tumor and metastases carried out, even having a vital prognosis.

Keywords

Malignant choroidal melanoma, Epithelioid cells, Retinal detachment, Enucleation, Exenteration, Radiotherapy, Photocoagulation.

Introduction

Malignant choroidal melanoma (MCM) is the most common primary intraocular tumor in adults with clinical manifestation around the age of 40-70 years, starting from choroidal melanocytes [1].

- Rare in black people
- MCM represents 85% of uveal tumors, with a higher incidence

in women (Hispanics), with variable pigmentation (intensely pigmented or amelanotic) [2].

- **MCM is frequently associated with serous retinal detachment, lipofuscin (orange spots) and sentinel episcleral vessels [3]**
- MCM metastasizes to the liver, lungs, bones, skin and CNS.

MCM can be primary tumor or secondary malignancy of a benign choroidal nevus; a malignant tumor is suspected if:

- The thickness of the choroid increases
- subretinal fluid is present
- Orange pigment appears

Risk factors

- sun exposure, UV exposure (excess tanning)
- light colored skin
- ocular melanocytosis
- gene suppression located on chromosome 3
- genetic predisposition, dysplastic nevus syndrome

Histopathologically

Histopathologically Callender classification - uveal MCM presents itself in 4 forms depending on the microscopic examination [1,2]:

- MM with "fusiform" cells type A, B - 45% with the best prognosis, with 10% survival rate.
- MM with epithelioid cells with large oval or round cells with a large nucleus with abundant acidophilic cytoplasm - 5% - with reserved prognosis.
- MM with mixed fusiform and epithelioid cells - 45% with intermediate prognosis
- Necrotic MM – 5% intermediate prognosis.

Clinical forms of MCM

MCM can be:

- Circumscribed (pedunculated) with the rupture of Bruch's membrane and by the growth of exudative retinal detachment tumor.
- Diffuse (flat) rare 5%, with slow extension in the uvea, with later symptoms.

According to size, MCM can be:

- small < 3 mm in thickness
- medium between 3-10 mm
- Large > 10 mm in thickness or > 16 mm in diameter.

The small-sized tumor is dome-shaped, growing, looking like a mushroom, rarely flat tumors, sometimes difficult to diagnose [4].

Clinical aspects in MCM

Symptoms [5]:

- asymptomatic
- 37% decrease in vision due to tumor location, cataract, induced astigmatism
- photopsia, metamorphopsia
- visual field changes
- eye pain rarely

Clinically:

- Choroidal tumor with lesional polymorphism (which could explain possible diagnostic errors and/or late diagnosis)
- Eye fundus examination with mydriasis shows:
 - prominent brownish subretinal tumor, with orange pigment on the surface - lipofuscin - pathognomonic sign for the malignant nature of the lesion
 - double vascular network: choroidal and tumoral [6]
- Associated signs: choroidal folds at the base of the tumor, cystoid retinal degeneration in the vicinity of the tumor, sub- or intraretinal hemorrhages, tumoral RD, hard exudates, vitreous hemorrhages
- Anterior pole signs:

- ocular and periocular congestion
- dilation of the episcleral vessels in the sector where the tumor is located
- dilated iris vessels in the tumor sector
- anisocoria due to hypertonia or paralytic touch
- anesthesia, corneal hypoesthesia in the vicinity of the tumor
- intra-ocular hypertension if the tumor invades the ciliary body

Complementary examinations to the complete ophthalmological examination with rigorously performed ophthalmological examination with mydriasis [5].

- ultrasound A, B which determines: the thickness of the tumor, the internal reflectivity of the tumor, the presence of extrascleralextension
 - low to medium reflectivity in: melanoma, nevus, choroidal effusion
 - medium to high reflectivity: neovascular choroidal membrane, cavernous hemangioma
- nonspecific FA
 - can show double circulation: choroidal and retinal, epifluorescent mass, punctate areas where fluorescein leaks in the late phases of FA
- CT, MRI of eyeball, orbit to highlight the extrascleral extension of the tumor, on MRI-MM it is hyperintense in T1 and hypointense in T2
- OCT
- transillumination
- eye fundus photos to assess documented tumor growth

Differential diagnosis of pigmented MCM:

- voluminous nevus that must be monitored for possible malignant degeneration
- melanocytoma with 0 or very low malignant potential
- pigmented retinal adenomas
- retinal hamartoma and RPE
- metastatic carcinoma
- age-related macular degeneration (AMD) exudative form with subretinal neovascularisation
- rhegmatogenous retinal detachment (RRD)
- choroid detachment
- congenital hypertrophy of the RPE

Differential diagnosis of amelanotic MCM:

- choroidal hemangioma
- choroidal osteoma
- posterior scleritis
- metastatic carcinoma

Metastases in choroidal MM occur through:

- hematogenous extension through vortex veins in: liver 92%, lungs, skin with increased risk of metastasis in tumors with:
 - height greater than 2 mm
 - proximity to the optic nerve
- cerebral extension by optic nerve (rare)

Evolution and complications in MCM

MCM evolution

Perforates Bruch's membrane and induces RD

- erodes the scleral wall and invades the orbit
- frequent distant metastases in the liver, but also lung, CNS, spinal cord, skin; the occurrence of metastases can be correlated with more intense tumor vascularization
- relapses after enucleation by tumor cells in the orbit
- exceptionally, spontaneous healing through tumor necrosis with foci of neoplastic regression with calcification

MCM has staged evolution: intraocular, secondary glaucoma, extraocular extension, distant metastases [1,3]

The ability to metastasize depends on:

- the size of the tumor
- tumor growth
- type of cells
- tumor vasculature

Complications:

- RD
- cataract, lens subluxation
- secondary glaucoma
- uveitis
- vitreous hemorrhage

Prognosis in MCM

Predictive factors for increased MCM:

- high thickness of the tumor
- the presence of subretinal fluid
- orange pigmentation
- punctate hyperfluorescence at FA
- the posterior edge of the tumor adjacent to the disc

Clinical elements of better prognosis of MCM:

- women, young subjects
- location at the posterior pole
- early enucleation

The prognosis of choroidal MM depends on:

- the cell type with the most reserved prognosis in the form with epithelioid cells, with survival rate below 30% in 5 years
- tumor size – large and diffuse tumors have a poor prognosis
- location
- the presence of vascular networks
- the age of the patient

Reserved prognostic factors:

- histologically
- numerous epithelioid cells
- vascular loops at the level of the tumor
- leukocyte infiltrations
- other factors
- chromosomal cellular abnormalities
- large tumors
- tumor extension
- previous tumor location
- age > 65 years

The mortality rate in MCM at 5 years is:

- Large melanomas 30-40%
 - o a basal diameter > 16 mm or thickness > 10 mm
 - o a scleral invasion 56%, extrascleral extension 8%
- medium-sized melanomas 20%
 - o height 2.5 – 10 mm, less than 16 mm in diameter
- small-sized melanomas 6%
 - o height 1-3 mm, diameter under 5 mm

Treatment of malignant choroidal melanoma

MCM treatment is:

- treatment of the primary tumor
- treatment of metastases.

COMS (Collaborative Ocular Melanoma Study) guides therapeutic options and evaluates treatment in MCM

- small tumors – height 1-3 mm, basal diameter 5-16 mm
 - observation with clinical follow-up and treatment according to the decision of the attending physician
- medium-sized tumors – height 2.5-10 mm, basal diameter > 16 mm
 - enucleation
 - radiotherapy/brachytherapy
- large tumors – height > 10 mm, basal diameter > 16 mm without metastases
 - enucleation
 - external radiotherapy 20 gy 5 days before and after enucleation

In choroidal MM, early diagnosis and appropriate treatment are necessary because the tumor has a definite vital prognosis [1,6]

Periodic follow-up of the tumor is necessary.

Conservative surgical treatment in iris tumors: sector iridectomy, iridocyclectomy, choriocyclectomy, partial choroidectomy. Small and medium-sized tumors, depending on the clinical stage, location, tumor extension, require the exact establishment of the possibility of maintaining the eyeball or whether enucleation is necessary.

- **if the eyeball is preserved, the indicated treatment of MM is**

- radiotherapy with:
 - o brachytherapy
 - o external radiation therapy
 - o proton radiotherapy
 - o “charged-particle” radiotherapy
- rare - laser photocoagulation; independent therapy, often combined with other therapeutic modalities

Conservative treatment of MCM [3,7]

Brachytherapy

- indicated in:
 - tumors less than 10 mm in thickness and 20 mm in diameter
 - medium-sized tumors with visual potential
 - failure of a PCL laser
 - MM with extraocular extension on painful eye without visual function (fpl)

- a radioactive plate applied to the episclera is used, fixing the focal radiation dose of the tumor with a cumulative dose of 80-100 Gy (estimated at the tumor apex) during 3-5 days or a cumulative dose of 50-70 Gy at the target volume level for 4-7 days
- radioisotopes used
 - small energy I125, Palladium106, Ruthenium103
 - high energy – CO60, Iridium192
- local recurrence if the indication is correct, may be possible, but rarely

Complications:

- radiation retinopathy, papillopathy
- cataract
- secondary neovascular glaucoma
- macular edema
- intravitreal hemorrhage

Complications of brachytherapy can reduce visual acuity (VA) by up to 55%, but results can be improved by intravitreal injection of bevacizumab. All patients will be periodically monitored with complete ophthalmological check-up at 6-12 months

External radiotherapy

- Indicated in tumors incompatible with brachytherapy by size and location less than 4 mm from the papilla and fovea

Complications:

- madarosa
- epiphora
- keratinization of the conjunctiva
- keratitis
- neovascular glaucoma
- exudative RD

Proton radiotherapy [8,9]

- allows preservation of the eyeball, with useful vision in 80% of patients
- can be an alternative to external beam radiotherapy or enucleation in large tumors
- complications:
 - radiation retinopathy, optic atrophy, macular edema, cataract, vitreous hemorrhage, glaucoma, retinal vein occlusion (RVO), scleral necrosis

Transpupillary thermotherapy – TTP – is indicated in small tumors, less than 3.5 mm, close to the fovea or papilla

- Transpupillary thermotherapy – TTP uses 810 nm diode laser, through a beam of laser energy that crosses the dilated pupillary opening and produces tumor tissue necrosis.

TTP treatment is indicated according to tumor size, growth rate, extrascleral extension + neovascular glaucoma + RD + metastases

- the treatment starts with impact points of 3 mm diameter, duration - 60 sec, 300 mV intensity
- the power is progressively increased (50 mV) until a discrete whitish area is obtained on the surface of the tumor
- the treatment is repeated every 3 months until an inactive chorioretinal scar is obtained

- the percentage of tumor regression is on average 20% if the indication was appropriate for the disease and the patient, small tumor, without local or metastatic tumor extension
- possible tumor recurrence
- TTP may be a therapeutic option in well-selected cases in MCM

Complications:

- retinal traction with preretinal fibrosis, retinobulbar vascular occlusions
- maculopathy
- changes in visual field
- there is a high percentage of local recurrence, explained by the persistence of unoccluded vessels in tumors > 3mm, achromatic, tumor close to the papilla
- TTP is done with an 810 nm diode laser; treatment is repeated every 3 months, tumor regression - 20%
- Other techniques:
 - photodynamic therapy
 - cryotherapy

Laser photocoagulation (LPC) [6,8,9] – can be used to eliminate (sometimes) small recurrences after conservative treatment (radiotherapy or local excisions)

- **Argon laser photocoagulation in MCM is a minor therapeutic method with limited indications and questionable efficiency**
- a maximum of 5% of patients with detected MCM benefit from LPC laser
- LPC laser can be indicated in the treatment of nevi responsible for edematous decompensation of the macular area
- The most common treatment in MCM is the surgical one with enucleation of the eyeball, which, however, must be performed in good time to prevent metastases
- The conservative treatment of pigmented choroidal tumors can be laser photocoagulation, often associated with other therapeutic indications, frequently with radiotherapy, or is used to resolve the side effects of irradiation (in cases of retinal ischemia induced by sector LPC radiotherapy or panphotocoagulation, it prevents neovascular glaucoma and vitreous haemorrhage) [7].
- LPC laser can (sometimes) eliminate small recurrences after conservative treatment (radiotherapy or local excisions).
- LPC laser can also be used for transscleral treatment of the tumor base with diode laser or Krypton laser
- The therapeutic efficiency can be enhanced by injecting indocyanine green which increases the wavelength absorption of the diode laser.

LPC laser is rarely used in ocular oncology; the most common LPC laser in tumors is associated with other therapeutic methods, to solve the side effects of irradiation and to prevent vision loss.

- The argon laser photocoagulant effect is often accompanied by scleral relapse, possibly due to the non-penetration of the laser impact to the sclera, using the transpupillary thermotherapy method as an adjunct to radiotherapy with precise indications.

Tumor exeresis

- is transretinal endoresection and transscleral resection indicated in very thick tumors for radiotherapy and under 16 mm diameter
- complications:
 - intraocular hypertension
 - macular hemorrhage
 - RD
 - cataract

Enucleation [1,5]

- It is the treatment of choice in large tumors, it is a radical, mutilating operation, which if NOT absolutely indicated, should be avoided if possible.
- It is indicated in large-sized tumors in the eye, with reduced/lost vision, in invasive, extensive tumors with extraocular evolution.
- The surgical alternative to enucleation could be transretinal resection of the tumor, but with appropriate indications.

Exenteration

- it is indicated in the extraocular extension of the tumor or in orbital recurrences

Treatment of liver metastases from MCM

- metastases can appear at a variable interval on average after 5 years
- metastases from MCM are generally refractory to systemic treatment and rarely produce a favorable and durable response
- the treatment of liver metastases is a prolonged palliative chemotherapeutic treatment for some patients in the form of local, locoregional treatment of metastases by localized excision, embolization by hepatic intraarterial injection

Cytotoxic chemotherapy with alkylating agents

- Cispatalin – the most active
- Sunitinib – is angiogenic and antiproliferative in patients with metastases from MCM
- Fotemustine – medium efficacy
- Dacarbazine – in patients at risk

Immunotherapy

- Interferon alfa 2b
- Dacarbazine – in high-risk patients
- Ipilimumab – monoclonal antibody
- MAPK inhibitors in recurrent, aggressive forms in long-term administration
- Vemurafenib
- Dabrafenib

Other therapies: hormonal therapy, biological therapy

MCM is the most common primary intraocular tumor in adults and has four histopathological forms, with: AB spindle cell 45%, with the best prognosis (survival 10%), epithelioid cells with reserved prognosis (survival 5%) with mixed cells and MCM necrotic, both with intermediate prognosis. MCM has the ability to metastasize depending on the size and location of the tumor, vascularity, cell type. Ophthalmoscopic examination shows the melanic tumor, with orange pigment on the surface, with a double vascular network, accompanied by: choroidal folds, tumor RD, and sometimes anterior pole signs, with possible intraocular hypertension, through tumor invasion of the ciliary body. MCM metastasizes locally, and distantly (liver, lungs, CNS, bone marrow), or recurrence is possible after enucleation through residual orbital tumor cells.

The treatment of MCM is the treatment of the primary tumor and the treatment of metastases. Small-sized tumors, depending on location, size, extension, can benefit from the possibility of preserving the eyeball, with correct indication of conservative treatment. The indication of choice in MCM is surgical treatment – enucleation, and in the case of tumor extension, exenteration.

Enucleation is indicated in large tumors, in eyes with low/lost vision, in invasive, extensive tumors. The surgical alternative to enucleation could be transretinal resection of the tumor (with appropriate indication). Exenteration is indicated in extensive or recurrent tumors. Distant metastases (liver, lung, CNS) require chemotherapeutic treatment (many liver metastases can be severe). Chemotherapy, immunotherapy is indicated in MCM.

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