Uveal melanoma diagnosis and current treatment options (Review)

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Abstract. Uveal melanoma is a rare condition accounting for only 5% of all primary melanoma cases. Still, it is the most frequently diagnosed primary intraocular malignant tumor in adults. Almost 90% of the tumors involve the choroid and only a small percentage affects the ciliary body or the iris. There is a consistent difference in incidence between different regions with individuals of northern European descent having a significantly higher risk as compared to Hispanics, Asians, and Blacks. Among the many risk factors, mutations in the G protein subunit alpha Q (*GNAQ*) or G protein subunit alpha 11 (*GNA11*) genes and different receptors are highly suggestive. While iris melanoma can easily be noticed by the patient itself or diagnosed at a routine slit-lamp evaluation, a consistent percentage of posterior uveal tumors are incidentally diagnosed at funduscopic evaluation as they can evolve silently for years, especially if located in the periphery. Uveal melanoma classifications rely on the tumor size (thickness and basal diameter) and also on intraocular and extraocular extension. The differential diagnosis with pseudomelanomas is carried out according to the tumor aspect and position. Iris melanoma has a better prognosis and a lower mortality rate as compared to choroidal melanoma that has a much higher rate of metastasis (50% of the patients) and a subsequent limited life expectancy from 6 to 12 months. While conservative therapeutic options for the primary tumor, relying on different surgical excision techniques and/or irradiation therapies, offer good local tumor control, the treatment options for metastatic disease, although numerous, are still inadequate in preventing a fatal outcome.

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Contents

1. Introduction

Uveal melanomas are uncommon but potentially life-threatening ocular conditions. They develop from melanocytes located in the highly pigmented uveal tract, the main oxygen, and nutriment provider of the retina. Anterior uveal melanomas originate in the iris while posterior uveal melanomas emerge from the choroid or the ciliary body. Among these tumors, choroidal melanoma is the most frequently diagnosed tumor (almost 90% of all uveal melanomas) followed by ciliary body melanoma (6% of the cases) and iris melanoma (4% of the cases) (1,2). Although uveal melanomas account for only 5% of all primary melanoma cases (90% located in the skin), they represent the most frequently diagnosed primary intraocular malignant tumor in adults.

While the incidence of cutaneous melanomas have continuously increased, the incidence of uveal melanomas has remained constant in the last decades across all continents. However, there are consistent differences in incidence between different areas worldwide (3). In the US, the incidence varies from 5.1 to 6 cases per million population per year, being highest in the southern latitudes (3). In Europe, the incidence of uveal melanomas is much higher (up to 8 cases per million population per year) in Caucacians of northern European descent (Scandinavia and Baltic States) and significantly lower in Italy (3.3 cases per million population per year), and Spain (1.9 cases

per million population per year) (4). Hispanics and Asians have a lower incidence while Black individuals have the lowest one. The relative risk of uveal melanoma has been estimated to be 1/1.2/5/19 in Blacks/Asians/Hispanics/Non-Hispanics, respectively (5).

There is no consistent sex-related difference; still, in epidemiological studies, the age-adjusted incidence has revealed that men have an increased predominance (5.8 per million in males as compared to 4.4 per million in females) (3). Uveal melanomas are uncommon in children. While the mean age for diagnosis has increased from 55 years of age to 62 years of age in Caucasians, in Asian countries uveal melanoma seems to appear at a younger age (6). Therefore, the mean age for diagnosis varies from 45 years of age (in the Chinese population) to 55 years of age (in the Japanese population).

To date, there are several risk factors identified in uveal melanoma development. Host susceptibility factors such as light-colored eyes, fair skin color, dysplastic nevus syndrome, ocular melanocytosis, and xeroderma pigmentosum have been confirmed as predisposing factors (7,8). In particular, a preexisting iris or choroidal nevus is of major concern as they can evolve into melanoma. The continuous nevus growth, together with the appearance of ectropion uveae and/or spontaneous hyphema (in the case of iris nevus) and subretinal fluid and orange pigmentation (in the case of choroidal nevus) highly suggests a transformation into melanoma (9). Excessive exposure to natural and artificial ultraviolet light and also to blue light have been suggested as risk factors (10). Patients with BRCA1-associated protein 1 (*BAP1*) mutation are considered to have a higher risk for developing uveal melanomas at a younger age (11). Most uveal melanomas have mutations in the G protein subunit alpha Q (*GNAQ*) or G protein subunit alpha 11 (*GNA11*) genes (90%) (12) and in the phospholipase C β4 (*PLCB4*) and the G-protein coupled receptor cysteinyl leukotriene receptor 2 (*CYSLTR2*) (13,14). In metastatic disease, there is a loss of chromosome 1p that leads to higher mortality when accompanied by the concurrent loss of chromosome 3 (15).

For this review, the authors performed an extensive literature search in the Medline electronic database, using the PubMed interface. The keyword combinations used were 'uveal melanoma', 'iris melanoma', 'ciliary body melanoma', 'choroidal melanoma' and, in turn, each of the following: 'diagnosis', 'treatment', 'metastatic'. We included articles in English, published from January 1, 1990 to February 28, 2021. After filters were applied (case report, classical article, guideline, journal article, meta-analysis, observational study, review, systematic review) a consistent number of 3,012 references resulted. Among these, 93 references were cited in this review.

2. Diagnosis of uveal melanoma

Iris melanoma is incidentally diagnosed at slit-lamp evaluation, usually much earlier (10 to 20 years) than other uveal melanomas. Sometimes, the patient solely notices the iris color changes (heterochromia). In most cases, the tumor is circumscribed, located inferiorly, and induces pupillary distortion (corectopia). Ectropion iridis, hyphema, secondary glaucoma, cataract, and extraocular extension are the most frequent complications. The intraocular pressure rise is the consequence of trabecular meshwork invasion or direct angle compression. The diagnosis of diffuse iris melanoma is more challenging and is often delayed due to the infiltrative pattern. Ring iris melanoma is a rare entity with angle location often simulating unilateral pigmentary glaucoma (16). The T1-T4 classification with further subgroups of iris melanoma, according to the American Joint Committee on Cancer Classification (AJCC), is based on tumor size (clock hours), tumor extension (ocular and extraocular), and complications (glaucoma) (17). While ultrasound biomicroscopy (UBM) and anterior segment optical coherence tomography (AS-OCT) are helpful tools in evaluating small anterior tumors, the B-scan ultrasonography can better evaluate larger tumors with posterior extension. Fine needle aspiration biopsy (FNAB) confirms the diagnosis (18).

The diagnosis of posterior uveal melanoma is usually performed by an experienced clinician during a routine slit-lamp biomicroscopy and/or indirect ophthalmoscopy under dilated pupil, as many tumors (especially ciliary body tumors) can silently grow for years and are totally asymptomatic (up to 40% of the cases). Most frequent complaints include floaters and photopsia. While tumors located in the periphery can reach consistent dimensions until visual field loss is noted, in locations closer to the macula and to the optic disc, the cystoid macular edema or secondary retinal detachment induces prompt visual loss. The funduscopic evaluation typically reveals a pigmented dome-shaped nodular mass, well-circumscribed, located under the retinal pigment epithelium. The degree of pigmentation can largely vary. In partially pigmented (30% of the cases) and amelanotic tumors (15% of the cases), the abnormalities of overlying retinal pigment epithelium and also the tumor vascularization can be easily observed. An accompanying massive exudative retinal detachment can hide the diagnosis. A mushroom-shaped aspect highly suggests that the Bruch membrane has been surpassed and is noted in 20% of the cases. Rarely, large tumors induce vitreous hemorrhage. Tumors located anteriorly show dilated overlying episcleral vessels ('sentinel vessels'), secondary glaucoma due to the anterior iris-lens diaphragm displacement or tumor extension into the angle, and cataract. Severe ocular pain due to posterior ciliary nerve involvement, transscleral tumor growth under the conjunctival, and proptosis due to orbital extension have also been reported (19).

According to the Collaborative Ocular Melanoma Study (COMS), choroidal melanoma is classified as small (largest basal diameter ≤16 mm, apical height between 1.5 and 2.4 mm), medium-sized (largest basal diameter ≤16 mm, apical height between 2.5 and 10 mm), and large (largest basal diameter ≤16 mm, apical height ≥10 mm) (20). The American Joint Committee on Cancer (AJCC) has updated the staging system according to size criteria (T1-T4), ciliary body involvement, and episcleral extension (21).

There is a consistent improvement in uveal melanoma diagnosis accuracy in the last decades, from around 20% to more than 99%, as indicated by the COMS (20). The 10 MHz B-scan ultrasonography is an essential evaluation tool in ocular oncology, easily revealing tumors with a thickness of more than 1.5 mm. It is particularly useful in opaque intraocular media. On B-scans, uveal melanomas have different shapes (collar-stud or mushroom appearance), have a low to moderate internal reflectivity, present a choroidal excavation,

and can be accompanied by a secondary retinal detachment. This technique is essential for measuring tumor dimensions, evaluating the extent, planning the treatment, and follow-up. The 40 MHz anterior UBM can visualize anterior uveal melanomas and differentiate them from those originating in the ciliary body. On A-scan there is a highly reflective anterior border followed by decreased amplitude as the tumor mass is acoustically hollow (positive kappa angle), and a significant final echo. Transillumination, which is particularly helpful in finding tumor borders, has a limited precision in partially pigmented and amelanotic tumors (19).

Fluorescein angiography (FA) and indocyanine green angiography (ICG) offer no pathognomonic signs in uveal melanomas. They have a limited contribution in differentiating choroidal nevi from small tumors but they can reveal, in larger tumors, a patchy fluorescent pattern (in FA) and the internal tumor vascularization known as 'double circulation pattern' (mainly in ICG). Fundus autofluorescence due to lipofuscin pigmentation is more intense than the autofluorescence of drusen usually seen in choroidal nevi. Orbital computed tomography (CT) and magnetic resonance imaging (MRI) with contrast are less sensitive diagnostic tools but help detect the extrascleral extension and in differentiating choroidal melanoma (which is enhanced by contrast) from choroidal detachment (no contrast enhancement) or choroidal osteoma (calcium detection). The Color Doppler ultrasound can differentiate the tumor from choroidal nevi due to the presence of a typical pulsatile blood flow at the tumor base. While regular spectral-domain OCT has limitations in accessing the tumor internal structure, the newer enhanced depth imaging spectral domain OCT can see deeper into the choroid and reveal the tumor, the thinned choriocapillaris, the accompanying retinal fluid, retinal changes, and retinal deposits (lipofuscin). An incisional biopsy is an invasive diagnostic tool involving the risk of complications and cancerous cell spreading and is currently indicated in uncertain cases only, such as amelanotic tumors (22).

On the contrary, fine-needle aspiration biopsy (FNAB) may soon become a standard procedure in conservatively treated melanomas as it provides the samples mandatory for genetic analysis with direct implications in prognosis and metastasis rates (23). Thus, according to gene expression profiling (GEP), ocular melanomas have been subdivided into 2 types. Class 1 tumors (further subdivided into class 1a and 1b), representing almost 50% of the cases, have a low and intermediate metastatic risk at 5 years (2 and 21%, respectively), while class 2 tumors have a significantly higher risk (72%) (23,24). The histological evaluation of the enucleated eye reveals 3 types of tumor cells: spindle A, spindle B, and epithelioid. The epithelioid has frequent mitotic figures, morphologic variations and is highly anaplastic. Thus, epithelioid cell melanoma and mixed cell melanoma are considered to have a significantly poorer prognosis as compared to spindle cell melanomas and necrotic melanomas (25).

3. Differential diagnosis and prognosis

The differential diagnosis of uveal melanoma is difficult. For circumscribed iris melanoma, it may include iris nevi, ocular melanocytosis, different iris nodules (sarcoidosis, juvenile xanthogranuloma), iris cysts, essential iris atrophy, iris foreign body, other iris tumors (leiomyoma), and metastasis. Diffuse iris melanoma should be mainly differentiated from diffuse iris nevi, ocular siderosis, pigmentary glaucoma, and congenital heterochromia. The most frequent posterior pseudomelanomas are represented by choroidal nevi, peripheral exudative hemorrhagic chorioretinopathy (PEHCR), congenital hypertrophy of the retinal pigment epithelium, hemorrhagic detachment of the retina or pigment epithelium (PED), choroidal detachment, circumscribed choroidal hemangioma, choroidal osteoma, and metastatic tumors (26).

Overall, iris melanoma has a better prognosis and a lower mortality rate as it develops metastases in only 2 to 7% of the cases, higher (10%) if there is mixed cellularity or ciliary body involvement. Choroidal melanoma has a much higher rate of metastasis (in almost 50% of the cases), mainly hematogenously, involving the liver (90%), the lungs, the brain, the kidneys, and the bones (27). The subsequent life expectancy is limited from 6 to 12 months (28). For many years, the tumor size, epithelioid type, ciliary body or optic nerve involvement, and extrascleral extension were considered as the main indicators for metastasis and mortality. Currently, the specific genetic profile (chromosome 3 deletion, chromosome 8q gain, BAP1 loss, chromosome 1p and 9q loss, Class 2 GEP) seems to be a better indicator for metastatic disease (29). Liver enzyme levels and chest X-rays should be routinely performed at the time of diagnosis to rule out the most frequent concomitant liver and/or lung metastasis (30).

4. Treatment options in uveal melanoma and metastatic disease

The main goals of ocular melanoma treatment are to destroy the tumor, prevent recurrence and metastasis, and conserve vision. While the treatment of primary uveal melanoma has constantly improved over time and different irradiation procedures have successfully replaced enucleation in selected cases, the therapeutic options for metastatic disease are still disappointing (29,30). The therapeutic attitude in primary uveal melanoma must take into account the tumor size, location and extension, the visual function, the status of the fellow eye, the age and health status of the patient, and last but not least the presence of metastasis (18,19).

Observation. Usually, small uveal lesions are closely monitored clinically and with sequential photography. While UBM is a helpful adjunct in monitoring iris lesions, B-scan ultrasonography is mandatory to detect any signs of growth of posterior lesions.

In the literature, iris nevi have a transforming rate estimated at 5% in 5 years and 11% in 20 years (31). On a larger series, the transformation rate was 2% at a mean follow-up of 5.6 years and 8% by 15 years (32). A systematical evaluation of predictive factors according to the mnemonic ABCDEF (A, age younger than 40 years; B, blood (hyphema); C, clock hour inferiorly (location); D, diffuse flat configuration; E, ectropion uveae, and F, feathery margins) was proposed to simplify the early detection of iris nevus growth into melanoma (32).

Choroidal nevi evolution must also be carefully monitored. Usually, choroidal nevi are a chronic condition easily

recognizable by the accompanying drusen and pigment epithelium atrophy on the surface and by the nonpigmented surrounding halo. They are detected in about 6% of the Caucasian population and have an annual conversion rate into melanoma that increases with age, estimated between 1 in 5,000 and 1 in 8,800 cases (33,34). Nevertheless, the appearance of visual symptoms, subretinal fluid, increasing thickness over 2 mm, orange pigmentation, absence of drusen and surrounding halo, ultrasound hollowness, and margin touching the optic disc are considered indicators for tumor conversion (9). Like in iris melanoma, the mnemonic TFSOM UHHD ('To Find Small Ocular Melanoma Using Helpful Hints'), derived from 'Thickness, Fluid, Symptoms, Orange pigment, Margin, Ultrasonographic Hollowness, Halo absence, and Drusen absence' was created by Shields *et al* to help practitioners to better evaluate the ocular melanoma risk factors (9,35). A careful evaluation of these features is of particular importance as the chance for tumor growth at 5 years is around 3% when no risk factors are encountered and over 50% when two or more factors are noted (35).

Prospective cohort studies suggest that early treatment is better than observation, in some patients, for preventing death from metastatic disease (36,37). In the particular case of elderly patients with active tumors, but with consistent comorbidities restricting therapeutic options or very low life expectancy, observation is a feasible choice (19).

Surgical treatments

Enucleation. This radical surgical technique, once the gold standard in the treatment of intraocular tumors, is still indicated in large uveal melanomas (>18 mm in basal diameter and >12 mm in thickness), in cases with total visual loss due to severe complications and in tumors refractory or recurrent to conservative treatments (16,19,22,30). Eyes with advanced orbital tumor extension are currently treated more conservatively avoiding orbital exenteration by combining enucleation with local radiation therapy (38). The Zimmerman-McLean-Foster hypothesis that enucleation accelerates mortality has been ruled out (39). Nevertheless, enucleation must be carefully performed as any excessive manipulation or injury to the affected eye during surgery carries the risk for tumor cell spreading into the bloodstream and orbital tissue, as suggested by the occurrence of orbital recurrences after enucleation. Performing external radiation before enucleation does not change the 10-year survival rate in large choroidal melanoma as compared to enucleation alone (40). The superiority of enucleation over conservative iodine-125 brachytherapy in reducing the risk of metastasis in medium-sized tumors has not been confirmed by the Collaborative Ocular Melanoma Study (COMS) in up to 12 years of follow-up (41).

Surgical excisions. Small iris melanoma is often successfully managed by sector iridectomy, especially if the tumor induces secondary glaucoma or interferes with the vision. Iridocyclectomy is preferred in rapidly growing iris tumors involving the angle (19,42). The surgical excision of choroidal melanomas has limited indications on small tumors only (19). Sclerouvectomy (transscleral resection) is a full-thickness excision including the sclera, the tumor, the choroid, and the retina. Usually, the scleral excision is around 3 mm larger than the melanoma. While banked sclera is mandatory for reconstruction, adjacent transscleral cryotherapy is necessary for retinal stability. Lamellar sclerouvectomy is less invasive to the retina than the previous technique (due to the partial-thickness scleral flap) but it carries a much higher risk for tumor reoccurrence (43). The most frequent complications of surgical excision are retinal detachment, vitreous hemorrhage, incomplete tumor removal, and cataract. Tumor endoresection during pars-plana vitrectomy is technically feasible but requires vast experience as the tumor margins are not always clearly visible. Although there is a major concern about the intraocular and extraocular tumor spread during surgery, a study found a lower rate of metastatic spread during endoresection (3.7%) as compared to the iodine 125 brachytherapy group (20.4%) (44). Nevertheless, the addition of local radiotherapy reduces the reoccurrence rate (45,46).

Irradiation therapies

Brachytherapy. Conservative treatment using a radioactive plaque temporarily sutured on the sclera adjacent to the tumor is one of the oldest (since the 1980's), most effective, and widespread methods for controlling medium-sized posterior uveal melanomas (47). It is also effective in iris melanoma treatment, but it has a significantly higher rate of cataract formation and eyelid scarring. The plaques have different sizes and shapes and must exceed the largest basal diameter of the tumor by 2 mm (48). The intraoperative usage of transillumination is mandatory to adequately temporarily attach to the sclera the plaque that will be removed after 3-7 days. Different isotopes with good tissue penetration are used to radioactively charge the plaques. Among them, ruthenium 106 is most frequently used in Europe while in the US iodine 125 is preferred. The usage of cobalt 60, iridium 192, palladium 103 and strontium 90 is less frequent (49). The time and the amount of energy delivered are calculated according to the tumor size. Thus, efficient, customized irradiation is performed at both the tumor base and apex with minimal adjacent tissue involvement. Brachytherapy is highly effective in tumor destruction so most of the treated melanomas show a consistent regression or even total flattening (47,50). While the tumor resistance rate widely varies between different centers, the local recurrence rate after iodine 125 or ruthenium 106 brachytherapy (in a diffuse manner or starting from the initial tumor margins) is estimated at 9.6% of cases and indicates the need for enucleation (51). Second double-dose brachytherapy has shown long-term efficacy in further decreasing or stabilizing the tumor size thus reducing the need for enucleation (52). A Swedish long-term patient survival study after plaque ruthenium 106 brachytherapy performed between 1980 and 1999, revealed excellent relative survival rates (97% at 1 year, 74% at 5 years, 64% at 10 years, 64% at 15 years, 62% at 20 years, 70% at 25 years, 83% at 30 years, 114% at 35 years and 200% at 40 years) and that 82% of uveal melanoma-related deaths occurred in the first decade after treatment (53). A retrospective evaluation of small choroidal melanomas treated with iodine 125 between 2004 and 2017 also showed that, after 3 years of follow-up, the survival rate was 97% with no metastatic events and that 69% of the patients retained visual acuity of at least 20/50 (54). Unfortunately, brachytherapy carries the risk of local complications such as cataract formation,

scleral necrosis, neovascular glaucoma, and dry eye (55). Radiation retinopathy is dependent on radiation dose and can occur in around 30% of the treated patients within 2 years of treatment (56). Radiation maculopathy and in particular radiation-induced macular edema can be efficiently controlled with intravitreal anti-vascular endothelial growth factor treatment or intravitreal dexamethasone implants (57). Radiation optic neuropathy is responsible for irreversible, sudden onset, visual loss within years after treatment of a tumor mainly located near the optic disc, most probably due to irreversible local vascular damage (58).

Proton beam radiotherapy. Developed in the early 1990s, charged-particle radiation is a newer conservative treatment, using protons or helium ions as charged particles to more precisely and much more safely deliver the desired amount of energy in different tumor parts. This method is a frequent conservative alternative to brachytherapy or enucleation for the treatment of unresectable or diffuse iris melanoma and in medium-sized or larger posterior melanomas if a charged-particle accelerator is available. The treatment is usually fractionated and is preceded, in the case of posterior uveal melanomas, by the initial scleral suture of tantalium rings that serve as radiopaque tumor reference markers. During the irradiation sessions, the head and eye must be carefully positioned. Although the efficacy seems to be similar to brachytherapy (59), there are major advantages due to more homogenous and focused treatment and less damage on the surrounding tissue (60). Still, radiation-associated complications can occur in time in almost 50% of the cases (61). Similar to brachytherapy, most of the tumors stop growing or regress after treatment. Also, the enucleation and the recurrence rates after treatment are comparable. The survival rate after charged-particle irradiation is comparable to that after enucleation (62,63).

Photon radiotherapy. (A recent meta-analysis of gamma knife radiosurgery as a primary treatment option in more than 1,000 uveal melanoma cases in the last 5 decades has shown that gamma knife radiosurgery is efficient in controlling the tumor in 96% of the cases with a 5-year survival rate of 76%. Still, further comparative randomized studies are needed to evaluate the position of this technique in the current therapeutic armamentarium (64).

Laser therapies

Direct laser photocoagulation. Direct laser photocoagulation of the uveal melanoma was the first conservative method introduced by Dr Meyer-Schwickerath in the early 50's (65). Today, this technique, with limited indication on small tumors only located at a distance from the fovea, is abandoned in many centers due to the modesttumor control and the increased rate of recurrence. Moreover, direct laser photocoagulation is associated with an increased risk of tumor extension through the Bruch's membrane, choroidal neovascularization, macular edema, retinal tractions and detachment, and vitreous hemorrhage (66).

Transpupillary thermotherapy (TTT). TTT uses a near-infrared diode laser. The local rise in temperature slightly over 45˚C offers better results than direct photocoagulation in the control of small melanomas and a lower tumor reoccurrence rate, especially when used in conjunction with brachytherapy (48). In a retrospective evaluation of primary TTT in choroidal melanoma, the tumor reoccurrence rate in a 2001-2012 group was 11% at 5 years and 15% at 10 years, significantly lower than in the previous group treated between 1995 and 2000 (67). Complications after TTT are noted in 44% of the cases and include retinal vascular occlusions, cystoid macular edema, epiretinal membranes, vitreous hemorrhage, optic disc atrophy, retinal traction and detachment (68).

Photodynamic therapy (PDT). PDT using verteporfin as a photosensitizer has been FDA approved in ophthalmology since the 2000's for the selective treatment of choroidal neovascularization secondary to various conditions due to minimal surrounding destruction. Primary PDT was found to be followed by complete tumor regression in 67% of small amelanotic choroidal melanomas at 5-year follow-up with no significant side effects on macular or optic nerve function (69). A recent meta-analysis of published studies found an overall 80% response rate to treatment, especially in small amelanotic tumors (70). While these results suggest that PDT is an effective primary treatment for small choroidal melanoma, especially in cases without pigmentation, further long-term studies are required for validation.

Treatments for metastatic disease. Although metastatic disease is detected in less than 1% of the patients with uveal melanoma at the time of initial diagnosis (71), a significant percentage of these patients will develop in time metastatic disease (31% of cases within 5 years, 45% within 15 years, and almost 50% within 25 years) (72). The dramatic decline in survival rate from 70% at 5 years for primary disease to only 8% at 2 years after metastatic disease as reported (73) confirms the need for an urgent treatment regimen and appropriate psycho-oncology support in such cases (74).

The usage of systemic chemotherapy has offered poor results suggesting that uveal melanoma is resistant to current chemotherapies. Conventional drugs (dacarbazine, temozolomide, and fotemustine), and many of the modern agents (paclitaxel, docosahexaenoic acid, and liposomal vincristine) have offered discouraging results, in monotherapy and also in combination. The most encouraging data have been noted with the combination of treosulfan and gemcitabine that showed a median survival of 14 months and an annual survival rate of 80% (75). Still, due to the frequent hematological, neurological, and pulmonary adverse effects that consistently lower the quality of life in these patients, systemic chemotherapy has not been routinely implemented for the treatment of metastatic disease (76).

Chemoimmunotherapy has also limited efficacy in uveal melanoma. The immune privilege of the eye may explain why promising preliminary results of recombinant interferon α-2b associated with the BOLD regimen (bleomycin, vincristine, lomustine, and dacarbazine) were not confirmed (77).

While immunotherapy alone using different agents (ipilimumab, pembrolizumab, or nivolumab) has shown limited results, the combination therapy (of ipilimumab with one of the previously mentioned agents) has offered

encouraging results with an overall survival rate of around 19 months (78-82). The side effects were found to vary from easily manageable skin reactions and pseudo-flu symptoms to more serious autoimmune colitis and thyroid and pituitary hormonal alterations. A consistent number of phase I and II clinical trials are currently underway to evaluate the efficacy and safety of novel immune-based therapies (such as cell-based and peptide vaccines, adoptive transfer of autologous TILs or CAR-T cells directed against human epidermal growth factor receptor 2) or different therapeutic combinations (pembrolizumab and entinostat, ipilimumab and melphalan PHP, ipilimumab and laparoscopic radiofrequency ablation) (50,83).

Molecular-targeted therapy seemed to be a suitable approach for uveal melanoma due to the distinctive genetic profile, with mutations in the *GNAQ* and *GNA11* genes stimulating cell proliferation (83). Unfortunately, several mitogen-activated protein kinase (MAPK) pathway inhibitors (used alone or in combination with chemotherapy) and also heat shock protein 90 inhibitors have failed to exhibit significant efficacy in clinical trials (50,84).

In regards to hepatic metastasis, liver-directed therapies, including intra-arterial chemotherapy with fotemustine, transarterial liver chemoembolization, and isolated hepatic perfusion have shown, besides their significant theoretical advantages, encouraging results in different studies (85-89). Different surgical laparoscopic excisions (alone or combined with radiofrequency ablation), liver radioembolization (using yttrium-90 microspheres), and liver thermotherapy have also shown promising results and are under evaluation (90-93).

5. Conclusions

The prognosis, survival rate, and quality of life in primary uveal melanoma tumors have significantly improved since the introduction of conservative irradiation therapies and surgical excisions. On the contrary, despite the consistent knowledge that has been acquired in the last decades regarding tumor genetics and pathogenesis (especially the biological and immunological mechanisms leading to tumor growth and spreading), there is to date no efficient therapeutic algorithm in controlling the metastatic disease responsible for a quick fatal outcome in almost 50% of the patients. Hopefully, the multiple clinical studies ongoing on this topic will soon confirm the encouraging preliminary results leading to more efficient and safer therapeutic protocols that will consistently increase the survival rate of these patients.

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Authors' contributions

DCB and ADM contributed to the study design, participated in the entire review process, and prepared the manuscript. CIB, FB, MAM, and MZ performed the bibliography research, and data analysis.. DEB and CMB contributed to the critical revision. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

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Competing interests

All the authors declare that they have no competing interests.

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