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Review Article

Comprehensive review of current approaches in the management of uveal melanoma

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Abstract

Uveal melanoma (UM), the most common primary intraocular malignancy in adults, poses significant challenges due to its aggressive nature and potential for metastasis, particularly to the liver. This review provides a comprehensive overview of the current management strategies for uveal melanoma, encompassing diagnostic advancements, therapeutic modalities, and emerging approaches. Early detection remains pivotal, with imaging techniques playing a critical role. Standard treatments such as enucleation, radiotherapy (including plaque brachytherapy and proton beam therapy), and laser therapies aim to balance tumor control with vision preservation. The limitations of systemic therapies and the unique biology of UM have led to the exploration of targeted therapies and immunotherapies. Agents such as selumetinib, tebentafusp, and immune checkpoint inhibitors show promise but face challenges in efficacy and patient selection. Despite these advances, there remains an unmet need for more effective systemic therapies and strategies to overcome treatment resistance. Emerging therapies, including combination regimens and next-generation immunotherapies, are under investigation, aiming to improve survival outcomes. Furthermore, adjuvant therapies and genetic profiling are shaping personalized medicine approaches, highlighting the importance of GNAQ, GNA11, and BAP1 mutations in prognosis and treatment decisions. Future research should focus on refining these strategies, addressing resistance mechanisms, and exploring the integration of liquid biopsy techniques for real-time monitoring. This review also addresses the role of surveillance strategies in detecting metastases and improving overall outcomes. By integrating current evidence and clinical advancements, this article aims to provide insights into optimizing the management of uveal melanoma and identifying avenues for future research**.** By identifying key gaps and potential breakthroughs, this article provides insights into optimizing the management of uveal melanoma and guiding future research directions.

Keywords: GNAQ, GNA11 Mutations, Advanced UM management, Targeted therapy, Tebentafusp, Radiotherapy, Genetic profiling, Metastasis.

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1. Introduction

Melanocytes in the eye give rise to the extremely aggressive malignancy known as uveal melanoma (UM). It is the most prevalent primary intraocular tumour in adults and is made up of the pigmented tissues of the iris (found in the anterior chamber of the eye), ciliary body, and choroid.[1] Choroidal melanomas, originating in the vascular choroid layer between the retina and sclera, make up 85%–90% of UM. On the other hand, melanomas of the ciliary body and iris are less frequent, occurring in 9% to 15% of cases. Iris melanomas appear as visible pigmented lesions while ciliary body melanomas located deeper are often detected late.[2] UM is primarily an adult malignancy with a reported annual incidence varying significantly across ethnic groups. The frequency is significantly greater among white people (6.3 per million) than among Hispanic populations (0.9 per million) and Black populations (0.24). This disparity underscores the importance of tailored screening programs and resource allocation to ensure early detection in high-risk groups. About 90% of UM form in the choroid, and the tumour starts from melanocytes, which are specialist pigment-producing cells found in the stroma of the uveal tract. The ciliary body accounts for about 7% of cases while 3% of cases of iris are least affected. These differences in site distribution reflect variations in cell

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density and exposure to potential oncogenic factors.[3] The incidence of UM varies from north to south in Europe, with northern regions like Norway and Denmark having over 8 cases per million yearly, whereas southern countries like Spain and Southern Italy have less than 2 cases per million. This geographical variation highlights the interplay of genetic, environmental, and lifestyle factors in UM pathogenesis, further emphasizing the need for region-specific preventive strategies.[4] The location of metastasis significantly impacts survival outcomes in individuals with metastatic UM. Up to 90% of cases involve the liver, making it the most frequent location of metastases. This predilection for hepatic involvement not only shapes the prognosis but also introduces unique therapeutic challenges, as the liver's microenvironment facilitates tumour progression and limits treatment efficacy. With a reported median survival of only 4 to 5 months, individuals with liver metastases unfortunately have a dismal prognosis. Furthermore, the 1-year survival rate for these patients is alarmingly low, ranging from 10% to 15%, underscoring the aggressive nature of the disease and the urgent need for effective systemic and targeted therapies.[5] Approximately half of patients with liver metastases from UM also exhibit extrahepatic involvement. While cases with metastases limited to extrahepatic sites are rare, these patients demonstrate a relatively better prognosis with a reported median survival of 19 to 28 months. The lungs (30%), bones (23%), and skin (17%) are the most often occurring extrahepatic metastases, indicating the disease's systemic character and capacity to impact a variety of organ systems.[6] A combination of phototherapy, radiation, and local tumour excision has essentially replaced enucleation, which was originally the accepted treatment for UM. The management approach for patients with UM once the diagnosis is confirmed, depends on factors such as tumour diameter, location and presence of complications like vitreous haemorrhage, retinal detachment or retinal involvement. These factors guide the choice of treatment to optimize outcomes and preserve eye function when possible.[2] Other factors influencing treatment decisions for UM include the patient's age, physical condition, economic situation and personal preferences. The lack of a proven treatment for metastatic UM remains a critical challenge, necessitating continued efforts in exploring novel therapeutic avenues. Regretfully, there isn't a proven, effective treatment plan for UM that has spread. Targeted therapy and immunotherapy have recently been the subject of several investigations as possible therapeutic approaches.[7] Light-colored eyes and skin, cutaneous and iris nevi or freckles, an inability to tan, BAP1 tumour predisposition syndrome, and exposure to UV radiation sources including tanning salons and arc welding are risk factors for UM.[8] Atypical cutaneous nevi, occupational contact to environmental irritants (such those found in welding and cooking), fair skin, nevus of Ota, periorbital dermal pigmentation, and cutaneous freckles are further known risk factors for UM.[9,10]

2. Pathophysiology and Progression

Melanocytes in three different uveal tissues—the iris (2% of cases), ciliary body (7%), and choroid (90%)—have oncogenic alterations that cause UM. These tissues, each with unique cellular environments and functions contribute to the varying clinical behaviours of UM. Genetic mutations in key oncogenes and tumour suppressor genes drive tumorigenesis and metastasis in these melanocytes.[11] There are just a few genetic changes that define it, and many of them have been well investigated. These genetic alterations affect surface receptor expression, intracellular signalling pathways, and ligand synthesis, all of which increase the risk of tumorigenesis and metastasis. Rarely do cutaneous melanomas show these changes, however they are frequently caused by activation of the MAPK pathway by mutations in BRAF (~50%), NRAS (10%–25%), or loss of function in NF1 (14%). Rather, point mutations in the G-protein α-subunit, which interfere with intracellular signalling and promote carcinogenesis, are the main characteristic of UM.[12] The genes GNAQ and GNA11 encode the α-subunit of G proteins, which work in tandem with GPCR. The exchange of GDP for GTP triggers G protein activation and subsequent signalling through downstream effector proteins, which in turn triggers signal transduction via G proteins and GPCRs. GTP has to be hydrolysed to GDP in order for the G protein to revert to its inactive form. GTPase activity depends on glutamine at position 209, according to studies, and mutations that interfere with this mechanism produce a constitutively active GTP-bound state. RAS oncogenes, which encode monomeric G proteins, have a mechanism with UM formation.

Table 1: Key genetic mutations and pathways in uveal melanoma

ime	Function	Pathway Affected	Clinical Relevance
GNAQ	Encodes G-protein α-subunit	MAPK, Hippo-YAP	Activates YAP/TAZ, promoting tumorigenesis and metastasis.
GNA11	Encodes G-protein α-subunit	MAPK, Hippo-YAP	Associated with aggressive tumor behavior.
BAP1	Tumor suppressor	DNA repair, chromatin regulation	Loss-of-function mutations correlate with poor prognosis.
SF3B1	Spliceosome component	RNA splicing	Linked to late-onset metastases with better prognosis.
EIF1AX	Translation initiation factor	Translation regulation	Associated with good prognosis in primary tumors.

Through Trio and downstream GTPases, GNAQ/GNA11 mutations increase YAP and TAZ activation. Additionally, epigenetic elements such as RNA alterations, histone modifications, and DNA methylation are involved.[13-15]

Clinical prognostic factors in UM are multifactorial and include several demographics, tumor-related, and pathological characteristics. Male gender and advanced age are known demographic variables associated with a worse prognosis for UM patients. Predicting the course of the disease also heavily relies on tumor-related characteristics, such as the size of the tumour and its precise placement inside the uvea. Tumours exhibiting a diffuse growth pattern, as opposed to more localized growth, tend to be associated with a more aggressive clinical course and poorer prognosis. An additional factor that raises the likelihood of metastasis and lowers survival is the presence of extraocular extension, which indicates invasion into nearby ocular or orbital tissues beyond the uvea. Furthermore, a standardised framework for determining the severity of the illness and forecasting patient outcomes is provided by the evolution of the tumour stage in accordance with the American Joint Committee on Cancer (AJCC) classification. Higher tumour stages, as defined by the AJCC system, are associated with a worse prognosis due to an increased risk of metastatic spread and diminished treatment efficacy. These prognostic factors, when considered collectively help to guide clinical decision-making and determine the most appropriate therapeutic approach for individual patients. Risk factors for a poor prognosis in UM include lymphocytes, tumor-infiltrating macrophages, epithelioid cell shape, mitotic activity, and the expression of HLA and IGF-1R.The pattern of the extravascular matrix including its type and organization also plays a critical role in determining the tumour's behavior and potential for metastatic spread. These histopathological features contribute significantly to the assessment of tumour aggressiveness and patient outcomes.[21]

2.1. Importance of early detection and management

Early detection and management of UM are crucial in improving both survival rates and quality of life. It is often diagnosed at advanced stages when it has spread to other parts of the body, particularly the liver, which significantly worsens prognosis. The ability to detect UM at an early, localized stage allows for more effective, less invasive treatment options potentially preserving both vision and the eye itself. Treatment strategies such as radiotherapy, phototherapy and local resection can be highly successful when the tumour is detected early, limiting the need for enucleation and minimizing long-term visual impairment.[16] Moreover, early detection of UM facilitates the monitoring of patients for metastasis. Metastatic disease, particularly to the liver, is a leading cause of mortality in UM patients. The median survival for those with metastatic UM is poor with studies reporting a median survival of 4 to 5 months and a 1-year survival rate of only 10-15%. Identifying UM early allows for closer monitoring and timely interventions that can slow or prevent metastasis, improving survival outcomes.[17] The detection of UM in its early stages also provides the opportunity for genetic and molecular profiling which can guide more personalized treatment approaches. UM has distinct genetic mutations, including GNAQ and GNA11, and other epigenetic alterations that can influence treatment decisions. By identifying specific mutations early, clinicians can tailor therapies, such as targeted therapies or immunotherapies that are most likely to be effective based on the genetic profile of the tumour. Early intervention is key to improving long-term outcomes by reducing the burden of the disease and ensuring a better quality of life for patients.[18]

3. Diagnosis of Uveal Melanoma

The most often used auxiliary imaging modalities for the clinical diagnosis of UM is ultrasound (USG). A useful instrument for evaluating UM's extraocular extension. When compared to the normal orbital tissue, regions of hyporeflectivity in this setting are suggestive of orbital tumour extension. The presence of such hyporeflective regions on USG suggests that the tumour has infiltrated beyond the choroid extending into the surrounding orbital structures.[19] On A-mode USG, the tumour often displays low to medium internal reflectivity, but on B-mode USG, it is viewed as an acoustically hollow, mushroom- or dome-shaped choroidal mass. In A-mode, the tumour's internal reflectivity decreases towards the sclera facilitating differentiation from hemangiomas which characteristically present with high reflectivity. The tumour looks acoustically hollow on B-mode because it is a hyper-echoic mass with a lower reflectivity than the nearby choroid. Together with possible orbital shadowing, choroidal excavation—which is more commonly seen in bigger tumors—may also be noticeable. This finding aids in the evaluation of the tumour's extent and the determination of appropriate management strategies.[20] It can be characterized by both intrinsic tumour circulation and the underlying choroidal circulation. The presence of this dual circulation pattern—comprising both the vascular supply from the tumour itself and the normal choroidal vessels—can be a crucial diagnostic feature. Confirming the diagnosis of UM may occasionally require observing this characteristic twin circulation or detecting leaking from the tumour vasculature. Such vascular abnormalities are typically assessed using techniques such as Doppler USG or fluorescein angiography, which provide detailed information on blood flow patterns and vascular leakage thereby assisting in distinguishing it from other intraocular pathologies. These characteristics may be seen via fundus fluorescein angiography, which helps distinguish them from other lesions. Additionally, it is employed in the identification and monitoring of post-brachytherapy problems such radiation retinopathy and radiation maculopathy.[22]

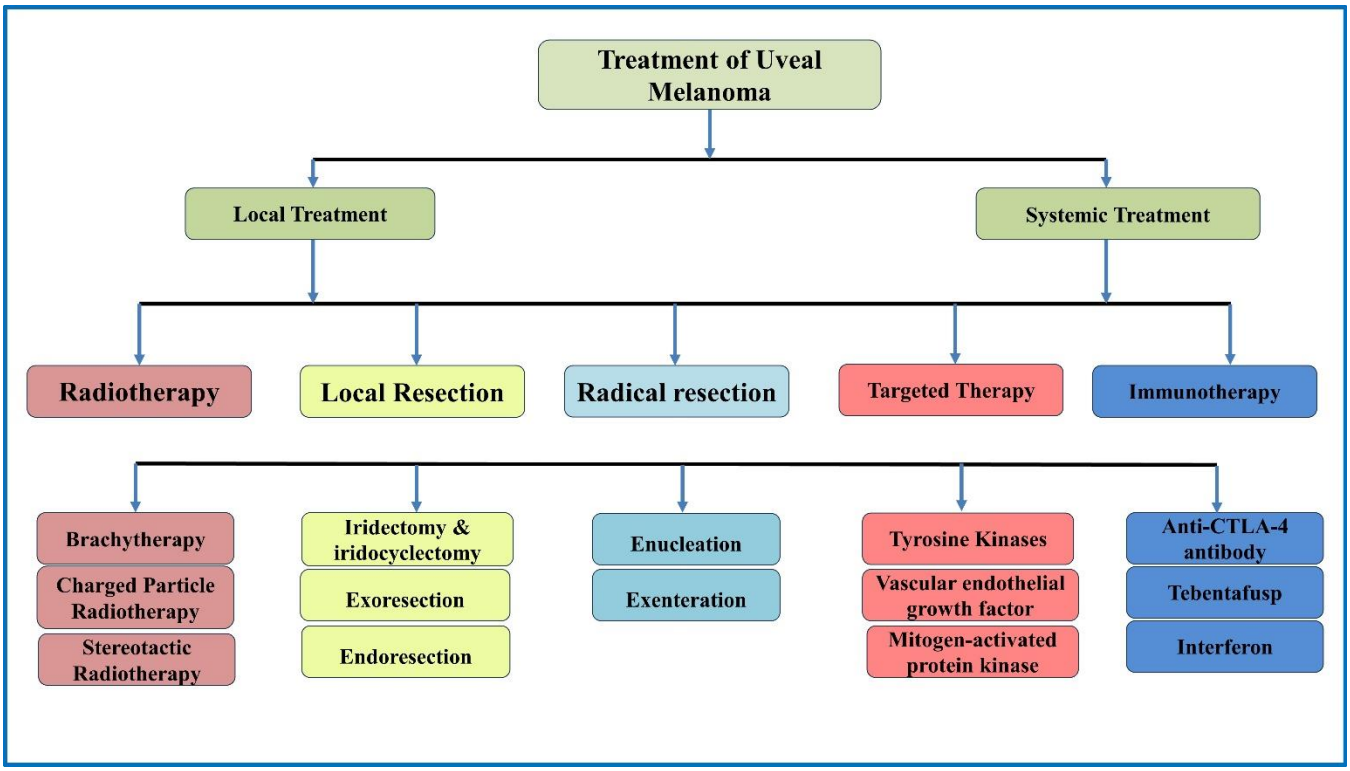

Figure 1: The diverse treatment approaches for managing uveal melanoma documented in earlier research.

3.1. Treatment of uveal melanoma

The treatment of UM is highly individualized and depends on several factors including the tumour's size, location, extent of extraocular involvement and the patient's overall health. The main treatment modalities for UM include:

3.1.1. Local treatment

It focuses on targeting and treating the tumour within the eye while attempting to preserve the eye and vision, if possible. The main local treatment options for UM include:(**Figure 1**)

3.1.1.1. Radiotherapy

One of the most successful globe-sparing therapies for UM is radiotherapy. It provides an alternative to enucleation, particularly for tumours that are localized or medium-sized. Brachytherapy, charged particle radiotherapy, and stereotactic radiotherapy are the primary types of radiation used for UM; each has unique benefits depending on the size, location, and other patient-specific characteristics of the tumour. The process via which radiotherapy affects UM is by using ionising radiation to cause cellular destruction. This radiation causes direct DNA damage in tumour cells, leading to cell lysis, senescence, or apoptosis, which are forms of programmed cell death. Additionally, radiation damages vascular endothelial cells within the tumour vasculature, resulting in tumour ischemia the restriction of blood supply followed by necrosis, shrinkage and eventual fibrosis of the tumour tissue. The combination of tumour cell death and vascular damage significantly impairs tumour growth and can result in substantial tumour regression.[28]

3.1.1.1.1. Brachytherapy

To provide targeted radiation while causing the least amount of harm to adjacent tissues, a radioactive plaque containing isotopes such as ruthenium-106 or iodine-125 is applied to the sclera above a tumour. This technique works especially well for tumours in the posterior eye that are close to important tissues like the optic nerve and macula. Radiation is delivered from the sclera to the tumour using a dish-shaped applicator that is sutured to the sclera. Iodine applicators work best on smaller tumours, whereas ruthenium applicators work best on tumours with a large basal diameter and height. Tumour volume, location, radioisotope type, and operator expertise are some of the variables that affect how well the therapy works.[2,23]

3.1.1.1.2. Charged Particle Radiotherapy

This method uses protons or carbon ions to irradiate the tumour. The use of charged particles allows for precise radiation delivery with minimal scatter to adjacent healthy tissues making it especially beneficial for tumors located deeper within the eye or near sensitive structures. Proton beam therapy is widely used in specialized centres for treating UM, especially when traditional brachytherapy may not be suitable. For patients with UM treated with proton beam irradiation (PBI), the 5-year survival rate stays over 80% and the globe-conserving success rate above 85%.[24] Seventy-four percent of patients keep their vision for ten

years after PBI therapy, and 87.5% of treated eyes have tumour control.[24,25] Complex tumours close to the macula or optic disc are especially well-suited for charged particle radiation because of its accurate targeting capabilities and ideal dose distribution. Furthermore, recurrent iris melanoma has been successfully treated with salvage proton beam therapy.[26]

3.1.1.1.3. Stereotactic radiotherapy

This non-invasive technique employs a combination of advanced imaging and precise radiation delivery systems to target the tumour with high accuracy. In order to precisely treat the cancer with radiation while avoiding damage to the orbital and ocular structures, it usually employs many beams positioned at various angles. It is frequently used for tumours that cannot be treated with conventional methods, such as those that are in hard-to-reach places or when maintaining eyesight is essential. With a 5-year local progression-free survival rate of 82% and a 2-year vision preservation rate of 75%, local control rates employing linear accelerator-based stereotactic fractionated photon radiation were found to be satisfactory.[27]

3.1.1.2. Local resection

Local resection for UM refers to the surgical removal of the tumour from the eye while attempting to preserve the surrounding ocular structures and when possible, visual function. This approach is typically reserved for cases where the tumour is small, localized and located in an accessible region of the eye such as the peripheral retina or the anterior segment.[29]

3.1.1.2.1. Iridectomy and iridocyclectomy

Iridectomy and iridocyclectomy are surgical procedures used to treat certain ocular conditions, including UM that involve the iris and ciliary body. Both procedures aim to remove tumour tissue while preserving the eye's integrity as much as possible. The mechanisms of these surgeries involve careful excision of tumour tissue and surrounding structures ensuring tumour control and minimizing the risk of recurrence. Incisions are made parallel to and 2-3 mm beyond the limbus to generate a sclero-corneal flap. Radial incisions are then made 2 mm beyond the tumor's boundaries. To access the cancer, a thorough keratectomy is carried out, followed by sector or peripheral iridectomies if necessary.[30,31]

3.1.1.2.2. Exoresection

Exoresection is an appropriate option for choroidal tumours with a basal diameter of less than 15 mm or iridociliary melanomas that include no more than 90° of the pars plicata. This procedure is typically considered for tumours that are localized and confined to specific, accessible areas, allowing for complete excision without significant risk of damaging surrounding ocular structures.[32] General anaesthesia and controlled systemic hypotension are necessary to reduce the risk of haemorrhage, and post-radiation exoresection is appropriate for ciliary body and big anterior choroidal tumours, as well as concealed iridociliary lesions with troubling characteristics including tumour progression or significant vascularization.[33] The technique known as "Partial Lamellar Sclerouvectomy" involves creating a scleral flap following a 270° peri-limbal incision and disinsertion of the surrounding extraocular muscles. The uveal tumour, along with the adjacent thin lamellar sclera, is carefully excised using a "no-touch" technique, ensuring that the underlying retina and vitreous remain undisturbed to prevent the spread of tumour cells into the surgical field.[34] For UM with a thickness of ≥6 mm, a research comparing exoresection with iodine-125 brachytherapy revealed that exoresection had superior visual acuity, while brachytherapy had greater adverse effects. However, the chance of a local recurrence was eight times higher after exoresection. The chance of tumour recurrence can be reduced by combining adjuvant plaque radiation with exoresection. Ru-106 plaque radiation has been shown to lower the incidence of recurrence in long-term follow-up investigations.[35,36]

3.1.1.2.3. Endoresection

Exoresection is technically challenging, and tumours close to the optic papilla or macula provide therapeutic issues since they may cause optic neuropathy or maculopathy. Patients with posterior choroidal melanomas that extend at least one disc diameter past the optic disc and fovea are candidates for endoresection. However, tumours with a base diameter larger than 15 mm are more likely to cause perioperative and postoperative problems. A typical three- or four-channel vitrectomy, posterior vitreous excision, and vitreous base removal are all part of the treatment. When the tumour is at its tallest, a retinotomy is done. To reduce haemorrhage, systemic hypotension should be maintained and intraocular pressure should be raised to 80 mmHg. During the operation, silicone oil and perfluorodecalin are frequently utilised; the silicone oil is usually eliminated three months later.[37]

3.1.1.3. Radical resection

Radical resection is a definitive surgical approach used in cases where the tumour is extensive has a high risk of recurrence or is located in an area where more conservative treatments are ineffective. It aims to achieve complete excision of the tumour although it may involve significant tissue removal and loss of organ function.

3.1.1.3.1. Enucleation

Enucleation was the main treatment for UM patients prior to the development of plaque radiation therapy. Currently, enucleation is typically reserved for advanced tumours with a diameter greater than 20 mm and a thickness exceeding 12 mm which are not effectively treated by radiation. Additionally, it is recommended for situations involving orbital invasion, total vision loss, or painful secondary

glaucoma. Four to six weeks after enucleation, a prosthetic eyeball can be implanted.

3.1.1.3.2. Exenteration

Orbital exenteration is recommended for recurring orbital tumours after prior enucleation or for advanced tumours including extraocular involvement. The eyeball, accompanying nerves, muscles, and fatty tissue are all removed during this treatment. To encourage quicker healing, an eyelid-preserving approach may be used if practical. Six to eight weeks following the exenteration, an orbital prosthesis may usually be inserted.[38]

3.1.2.. Systemic treatment

3.1.2.1. Targeted therapy

Targeting certain molecules implicated in tumour growth is the goal of molecular targeted therapy, a very focused therapeutic strategy. It modifies the biological behaviour of tumour or stromal cells by inhibiting signal transduction pathways. Molecular targeted therapy can be used as a monotherapy, targeting specific molecular pathways involved in tumor growth or in combination with other treatments like chemotherapy, radiation or immunotherapy. When combined, it enhances treatment efficacy by overcoming resistance mechanisms, improving tumour response and potentially increasing overall survival. This approach is tailored to the tumour's genetic profile, optimizing therapeutic outcomes.[39] (**Table 2**)

Table 2: Comparative analysis of treatment modalities for uveal melanoma

Treatment Modality	Efficacy	Survival Rates	Risks/Complications
Radiotherapy	Effective for localized and medium-sized tumors; high tumor control rates.	5-year survival: >80% (Proton Beam Therapy); Globe-sparing rate: >85% (Proton Beam Therapy).	Radiation retinopathy, optic neuropathy, secondary glaucoma, cataract, and potential vision loss.
Brachytherapy	Precise radiation for small and posterior tumors; effective tumor control.	Long-term tumor control in 85%–95% of cases depending on tumor size and location.	Local recurrence, damage to adjacent ocular structures (optic nerve, macula), and increased risk of secondary glaucoma and radiation-related complications.
Charged Particle Therapy	Superior dose distribution for deep-seated or complex tumors.	5-year survival: >80%; Vision preservation: ~74% over 10 years.	Tissue necrosis, persistent inflammation, and radiation-induced cataracts.
Stereotactic Radiotherapy	Effective for inaccessible or challenging locations.	Local progression-free survival: ~82% (5 years); Vision preservation: ~75% (2 years).	Local recurrence, inflammation, and damage to adjacent ocular and orbital structures.
Surgical Resection	Suitable for localized tumors; effective when paired with adjuvant therapies.	Tumor control rates vary based on surgical type and location; adjunct radiation reduces recurrence.	High recurrence rates without adjuvant therapy, significant visual impairment, and intraoperative complications (e.g., hemorrhage).
Targeted Therapy	Moderate efficacy for molecularly targeted tumors (e.g., c-kit, VEGF).	Limited survival benefit in advanced/metastatic cases.	Adverse effects like cytopenia, fatigue, gastrointestinal disturbances, and drug resistance.
Immunotherapy	Promising results with tebentafusp; limited efficacy with CTLA-4 inhibitors.	Tebentafusp: 1-year survival ~65%; Ipilimumab/Nivolumab: Median OS ~11.8 months in selected patients.	Immune-related adverse events: colitis, dermatitis, pneumonitis, endocrinopathy; limited efficacy in immune-privileged UM environment.
Enucleation	Effective for large or advanced tumors; no vision preservation.	Survival unaffected compared to radiotherapy in early-stage tumors; used when tumor is >20mm in diameter.	Complete loss of vision; psychological impact; prosthetic complications.
Exenteration	Reserved for extensive orbital involvement or recurrence post-enucleation.	Not applicable; used as a last resort in locally advanced disease.	Loss of orbital structures, severe disfigurement, and delayed healing.

3.1.2.2. Tyrosine kinases

For anti-tumor molecular targeted treatment in UM, tyrosine kinases are important targets. Many cancers, including metastatic UM, overexpress the c-kit protein, a crucial membrane-bound tyrosine kinase receptor. It has been shown that the FDA-approved inhibitor imatinib mesylate inhibits c-kit activity. Research demonstrates that imatinib mesylate prevents human UM cells from proliferating and invading in vitro.[40] Patients with metastatic UM were given 400 mg of imatinib mesylate twice a day as part of a phase II clinical study. The results indicated a modest prolongation of survival. However, the trial was discontinued due to the occurrence of adverse events.[41]

3.1.2.3. Vascular endothelial growth factor

Angiogenesis and VEGF expression are well-established processes of tumour formation, and their possible involvement in UM has been well investigated. Seventy-four enucleated UM eyes that had not had initial therapy were analysed in one research. The VEGF quantity in the aqueous humour of UM specimens was considerably greater than that in non-neoplastic eyes having cataract surgery, the researchers discovered.[42] Two important histological measures, tumour thickness and basal diameter, showed a favourable connection with VEGF expression. Additionally, later research revealed that bevacizumab administered intraperitoneally inhibited cancer development and liver metastases in mice in a dose-dependent manner.[43]

3.1.2.4. Mitogen-activated protein kinase

In 80% of big tumours, the MAPK pathway is the focus of the therapy trametinib for metastatic ovarian cancer. It has undergone testing both alone and in conjunction with chemotherapy. In patients with metastatic UM, selumetinib and chemotherapy were examined in multicenter phase II research. While overall survival was 11.8 months and 9.1 months, respectively, selumetinib had a median progression-free survival of 15.9 weeks. Of patients treated with selumetinib, 49% had tumour shrinkage, while 97% had side effects. For metastatic UM, a follow-up international double-blind phase III study evaluated the safety and effectiveness of selumetinib with dacarbazine. According to the results, selumetinib improved the objective remission rate and prolonged progression-free survival in a subgroup of patients by enhancing the therapeutic efficacy of dacarbazine.[44,45]

3.1.3. Immunotherapy

Because UM has a low mutational load and the ocular environment is immune-privileged, immunotherapy's clinical effectiveness is restricted when compared to cutaneous melanoma (CM), especially when checkpoint inhibition is used. The new good findings of tebentafusp show that immunotherapeutic approaches remain promise despite the inferior results seen with checkpoint inhibitors.

3.1.3.1.. Anti-CTLA-4 antibody

In order to prevent tumour progression, ipilimumab, a selective inhibitor of cytotoxic T-lymphocyte antigen-4 (CTLA-4), strengthens T-lymphocyte-mediated immune responses. Danielli et al. assessed its safety and effectiveness in UM patients.[46] In clinical studies, ipilimumab demonstrated potential in treating UM. In one study, 30 patients received 10 mg/kg intravenously and were assessed at 12, 24, and 36 weeks, showing disease control and improved overall survival, However, three individuals experienced severe side effects, including as thrombocytopenia and diarrhoea. 52 patients were given ipilimumab at a dose of 3 mg/kg for four cycles in a multicenter study conducted by Zimmer et al. At 12 and 24 weeks, 47% and 21% of patients, respectively, had disease stability, whereas 66% had complications, including 19 high-grade events. Furthermore, in metastatic UM, ipilimumab with nivolumab, a PD-1 inhibitor, showed encouraging action, generating notable and long-lasting effects.[47]

3.1.3.2. Tebentafusp

Tebentafusp is a bispecific fusion protein designed to target gp100, a melanocytic antigen present in both cutaneous and UM. It works by directing CD3+ T cells towards gp100-expressing melanoma cells, which results in T-cell-mediated cytolysis. A first-in-human (FIH) phase I study of tebentafusp was carried out by Middleton et al. in 84 patients with metastatic melanoma, 16 of whom had UM. Among the evaluable UM patients, 14% achieved a partial response, while 57% maintained clinical control for at least 16 weeks. In the dose-escalation cohort, erythema, pruritus, fever, and periorbital oedema were the most frequent side events. In both UM and cutaneous patient groups, tebentafusp showed a 1-year overall survival rate of 65%, indicating high tolerability and clinical efficacy overall in advanced UM.[48]

3.1.3.3. Interferon

When 121 high-risk UM patients received interferon (IFN)-α-2a for two years, there was no discernible increase in survival rates when compared to those receiving enucleation or radiation treatment. Likewise, Richtig et al. assessed adjuvant IFN-α-2b's safety and effectiveness in 39 UM patients. In 18 cases, side symptoms such leukopenia, heart problems, thrombocytopenia, liver malfunction, or fainting necessitated dose reductions. Eight individuals had their treatment stopped because of serious side effects or the spread of the disease. IFN treatment did not appear to improve survival in UM patients.[49]

4. Conclusion

Uveal melanoma remains a formidable clinical challenge due to its aggressive nature, metastatic potential, and limited treatment options for advanced disease. Current management strategies, including surgical interventions, radiotherapy, and systemic therapies, have significantly improved localized

tumor control and patient survival. However, the prognosis for metastatic uveal melanoma remains dismal, highlighting the urgent need for innovative therapeutic strategies.

Adopting genetic and molecular profiling should be prioritized to facilitate personalized medicine, enabling targeted therapies and immunotherapies to deliver more precise and effective outcomes. Integrating early diagnostic tools, optimized surveillance protocols, and emerging therapies into clinical practice can enhance disease management. For instance, identifying robust early diagnostic biomarkers could significantly improve the detection and treatment of high-risk cases, potentially altering the disease trajectory.

Critical gaps remain, such as understanding the molecular pathways driving tumor progression and resistance mechanisms. These gaps demand rigorous research to develop innovative combinations of therapies, including targeted agents and immunotherapeutic approaches. Clinical trials evaluating novel agents will be pivotal in addressing these unmet needs.

A multidisciplinary approach, combining expertise in ophthalmology, oncology, and genetics, is essential to improve the quality of life and survival for patients with this rare but challenging malignancy. To this end, fostering collaboration across specialties and emphasizing the integration of cutting-edge research into routine clinical practice should be a top priority for advancing patient care.

5. Source of Funding

None.

6. Conflict of Interest

None.

References

1. Jager MJ, Shields CL, Cebulla CM, Abdel-Rahman MH, Grossniklaus HE, Stern MH. Uveal melanoma. *Nat Rev Dis Primers*. 2020;6(1):24. https://doi.org/10.1038/s41572-020-0158-0.
2. Bai H, Bosch JJ, Heindl LM. Current management of uveal melanoma: A review. *Clin Exp Ophthalmol.* 2023;51(5):484–94. https://doi.org/10.1111/ceo.14214.
3. Spagnolo F, Caltabiano G, Queirolo P. Uveal melanoma. *Cancer* Treat Rev. 2012;38(5):549–53.
4. Carvajal RD, Sacco JJ, Jager MJ, Eschelman DJ, Olofsson Bagge R, Harbour JW, et al. Advances in the clinical management of uveal melanoma. *Nat Rev Clin Oncol.* 2023;20(2):99–115. https://doi.org/10.1038/s41571-022-00714-1.
5. Singh AD, Borden EC. Metastatic uveal melanoma. Ophthalmol Clin North Am. 2005;18(1):143–50. https://doi.org/10.1016/j.ohc.2004.07.003.
6. Bedikian AY. Metastatic uveal melanoma therapy: current options. *Int Ophthalmol Clin.* 2006;46(1):151–66. https://doi.org/10.1097/01.iio.0000195852.08453.de
7. Toro MD, Gozzo L, Tracia L, Cicciù M, Drago F, Bucolo C, et al. New Therapeutic Perspectives in the Treatment of Uveal Melanoma: A Systematic Review. *Biomedicines.* 2021;9(10):1311. https://doi.org/10.3390/biomedicines9101311.
8. Weis E, Aghazadeh H, Roelofs K, Agi J. Sunlamp use is a risk factor for uveal melanoma: a meta-analysis. *Can J Ophthalmol*. 2022;57(2):105–11. https://doi.org/10.1016/j.jcjo.2021.02.041.
9. Nayman T, Bostan C, Logan P, Burnier MN Jr. Uveal Melanoma Risk Factors: A Systematic Review of Meta-Analyses. *Curr Eye Res.* 2017;42(8):1085–93. https://doi.org/10.1080/02713683.2017.1297997.
10. Singh AD, De Potter P, Fijal BA, Shields CL, Shields JA, Elston RC. Lifetime prevalence of uveal melanoma in white patients with oculo(dermal) melanocytosis. *Ophthalmology*. 1998;105(1):195–8. https://doi.org/10.1016/s0161-6420(98)92205-9.
11. Shields CL, Kaliki S, Furuta M, Mashayekhi A, Shields JA. Clinical spectrum and prognosis of uveal melanoma based on age at presentation in 8,033 cases. *Retina*. 2012;32(7):1363-72. https://doi.org/10.1097/IAE.0b013e31824d09a8.
12. Mazloumi M, Vichitvejpaisal P, Dalvin LA, Yaghy A, Ewens KG, Ganguly A, et al. Accuracy of The Cancer Genome Atlas Classification vs American Joint Committee on Cancer Classification for Prediction of Metastasis in Patients With Uveal Melanoma. *JAMA Ophthalmol.* 2020;138(3):260–7. https://doi.org/10.1001/jamaophthalmol.2019.5710.
13. Kalinec G, Nazarali AJ, Hermouet S, Xu N, Gutkind JS. Mutated alpha subunit of the Gq protein induces malignant transformation in NIH 3T3 cells. *Mol Cell Biol.* 1992;12(10):4687–93. https://doi.org/10.1128/mcb.12.10.4687-4693.1992.
14. Feng X, Degese MS, Iglesias-Bartolome R, Vaque JP, Molinolo AA, Rodrigues M, et al. Hippo-independent activation of YAP by the GNAQ uveal melanoma oncogene through a trio-regulated rho GTPase signaling circuitry. *Cancer Cell.* 2014;25(6):831–45. https://doi.org/10.1016/j.ccr.2014.04.016.
15. Krantz BA, Dave N, Komatsubara KM, Marr BP, Carvajal RD. Uveal melanoma: epidemiology, etiology, and treatment of primary disease. *Clin Ophthalmol*. 2017;11:279–89. https://doi.org/10.2147/opth.s89591.
16. Bronkhorst IH, Ly LV, Jordanova ES, Vrolijk J, Versluis M, Luyten GP, et al. Detection of M2-macrophages in uveal melanoma and relation with survival. *Invest Ophthalmol Vis Sci.* 2011;52(2):643–50. https://doi.org/10.1167/iovs.10-5979.
17. Bidard FC, Madic J, Mariani P, Piperno-Neumann S, Rampanou A, Servois V, et al. Detection rate and prognostic value of circulating tumor cells and circulating tumor DNA in metastatic uveal melanoma. *Int J Cancer.* 2014;134(5):1207–13. https://doi.org/10.1002/ijc.28436.
18. Tarlan B, Kıratlı H. Uveal Melanoma: Current Trends in Diagnosis and Management. *Turk J Ophthalmol.* 2016;46(3):123–37. https://doi.org/10.4274/tjo.37431.
19. Shields JA, Shields CL. *Intraocular tumors: an atlas and textbook*. Lippincott Williams & Wilkins. 2008.
20. Kivelä T. Diagnosis of uveal melanoma. *Developments in ophthalmology*. Karger. 2011. https://doi.org/https://doi.org/10.1159/000330613
21. Singh AD, Shields CL, Shields JA. Prognostic factors in uveal melanoma. *Melanoma Res*. 2001;11(3):255–63. https://doi.org/10.1097/00008390-200106000-00007.
22. Herwig MC, Grossniklaus HE. Pathology of Choroidal melanoma. In *Retina* WB Saunders. 2013:2254–66. https://doi.org/10.1016/B978-1-4557-0737-9.00142-9
23. Shields CL, Shields JA, Cater J, Gündüz K, Miyamoto C, Micaily B, et al. Plaque radiotherapy for uveal melanoma: long-term visual outcome in 1106 consecutive patients. *Arch Ophthalmol.* 2000;118(9):1219–28. https://doi.org/10.1001/archopht.118.9.1219.
24. Bellocq D, Roy P, Kodjikian L, Mathis T, Nguyen AM, Herault J, et al. 20-year assessment of metastatic latency and subsequent time to death after proton therapy for uveal melanomas. *Melanoma Res.* 2020;30(3):272–8. https://doi.org/10.1097/CMR.0000000000000519.
25. Toyama S, Tsuji H, Mizoguchi N, Nomiya T, Kamada T, Tokumaru S, et al. Working Group for Ophthalmologic Tumors. Long-term results of carbon ion radiation therapy for locally advanced or

unfavorably located choroidal melanoma: usefulness of CT-based 2-port orthogonal therapy for reducing the incidence of neovascular glaucoma. *Int J Radiat Oncol Biol Phys*. 2013;86(2):270–6. https://doi.org/10.1016/j.ijrobp.2012.12.022.

26. Riechardt AI, Klein JP, Cordini D, Heufelder J, Rehak M, Seibel I, Joussen AM. Salvage proton beam therapy for recurrent iris melanoma: outcome and side effects. *Graefes Arch Clin Exp Ophthalmol.* 2018;256(7):1325–32. https://doi.org/10.1007/s00417-018-3929-5.
27. Akbaba S, Foerster R, Nicolay NH, Arians N, Bostel T, Debus J, et al. Linear accelerator-based stereotactic fractionated photon radiotherapy as an eye-conserving treatment for uveal melanoma. *Radiat Oncol.* 2018;13(1):140. https://doi.org/10.1186/s13014-018-1088-9.
28. Groenewald C, Konstantinidis L, Damato B. Effects of radiotherapy on uveal melanomas and adjacent tissues. *Eye (Lond).* 2013;27(2):163–71. https://doi.org/10.1038/eye.2012.249.
29. Damato BE. Local resection of uveal melanoma. Current concepts in uveal melanoma. Karger. 2012;49:66–80. https://doi.org/https://doi.org/10.1159/000328261
30. Klauber S, Jensen PK, Prause JU, Kessing SV. Surgical treatment of iris and ciliary body melanoma: follow-up of a 25-year series of patients. *Acta Ophthalmol.* 2012;90(2):122–6. https://doi.org/10.1111/j.1755-3768.2010.01889.x.
31. Rahmi A, Mammar H, Thariat J, Angellier G, Herault J, Chauvel P, et al. Proton beam therapy for presumed and confirmed iris melanomas: a review of 36 cases. *Graefes Arch Clin Exp Ophthalmol.* 2014;252(9):1515–21. https://doi.org/10.1007/s00417-014-2735-y.
32. Gündüz K, Bechrakis NE. Exoresection and endoresection for uveal melanoma. *Middle East Afr J Ophthalmol.* 2010;17(3):210–6. https://doi.org/10.4103/0974-9233.65494.
33. Shields JA, Shields CL, Shah P, Sivalingam V. Partial lamellar sclerouvectomy for ciliary body and choroidal tumors. *Ophthalmology.* 1991;98(6):971–83. https://doi.org/10.1016/s0161-6420(91)32194-8.
34. Shields JA, Shields CL. Surgical approach to lamellar sclerouvectomy for posterior uveal melanomas: the 1986 Schoenberg lecture. *Pediatric Ann*. 1988;17(11):774–80. https://doi.org/10.3928/0090-4481-19881101-04
35. Kivelä T, Puusaari I, Damato B. Transscleral resection versus iodine brachytherapy for choroidal malignant melanomas 6 millimeters or more in thickness: a matched case-control study. *Ophthalmology.* 2003;110(11):2235-44. https://doi.org/10.1016/j.ophtha.2003.02.001.
36. Bechrakis NE, Petousis V, Willerding G, Krause L, Wachtlin J, Stroux A, Foerster MH. Ten-year results of transscleral resection of large uveal melanomas: local tumour control and metastatic rate. *Br J Ophthalmol.* 2010;94(4):460–6. https://doi.org/10.1136/bjo.2009.162487.
37. Rice JC, Liebenberg L, Scholtz RP, Torr G. Fatal air embolism during endoresection of choroidal melanoma. *Retin Cases Brief Rep*. 2014;8(2):127–9. https://doi.org/10.1097/ICB.0000000000000021.
38. Blanco PL, Lim LA, Miyamoto C, Burnier MN. Uveal melanoma dormancy: An acceptable clinical endpoint? Melanoma Res. 2012;22(5):334–40. https://doi.org/10.1097/CMR.0b013e328357bea8.
39. Hamza HS, Elhusseiny AM. Choroidal melanoma resection. *Middle East Afr J Ophthalmol*. 2018;25(2):65–70. https://doi.org/10.4103/meajo.meajo_73_18
40. Pereira PR, Odashiro AN, Marshall JC, Correa ZM, Belfort R Jr, Burnier MN Jr. The role of c-kit and imatinib mesylate in uveal melanoma. *J Carcinog*. 2005;4:19. https://doi.org/10.1186/1477-3163-4-19.
41. Penel N, Delcambre C, Durando X, Clisant S, Hebbar M, Negrier S, et al. O-Mel-Inib: a Cancéro-pôle Nord-Ouest multicenter phase II trial of high-dose imatinib mesylate in metastatic uveal melanoma. *Invest New Drugs*. 2008;26(6):561–5. https://doi.org/10.1007/s10637-008-9143-2.
42. Missotten GS, Notting IC, Schlingemann RO, Zijlmans HJ, Lau C, Eilers PH, et al. Vascular endothelial growth factor a in eyes with uveal melanoma. *Arch Ophthalmol*. 2006;124(10):1428–34. https://doi.org/10.1001/archopht.124.10.1428.
43. Yang H, Jager MJ, Grossniklaus HE. Bevacizumab suppression of establishment of micrometastases in experimental ocular melanoma. *Invest Ophthalmol Vis Sci*. 2010;51(6):2835-42. https://doi.org/10.1167/iovs.09-4755.
44. Khalili JS, Yu X, Wang J, Hayes BC, Davies MA, Lizee G, et al. Combination small molecule MEK and PI3K inhibition enhances uveal melanoma cell death in a mutant GNAQ- and GNA11-dependent manner. *Clin Cancer Res*. 2012;18(16):4345-55. https://doi.org/10.1158/1078-0432.CCR-11-3227.
45. Carvajal RD, Sosman JA, Quevedo JF, Milhem MM, Joshua AM, Kudchadkar RR, et al. Effect of selumetinib vs chemotherapy on progression-free survival in uveal melanoma: a randomized clinical trial. *JAMA*. 2014;311(23):2397–405. https://doi.org/10.1001/jama.2014.6096.
46. Danielli R, Ridolfi R, Chiarion-Sileni V, Queirolo P, Testori A, Plummer R, et al. Ipilimumab in pretreated patients with metastatic uveal melanoma: safety and clinical efficacy. *Cancer Immunol Immunother.* 2012;61(1):41-8. https://doi.org/10.1007/s00262-011-1089-0.
47. Pelster MS, Gruschkus SK, Bassett R, Gombos DS, Shephard M, Posada L, et al. Nivolumab and Ipilimumab in Metastatic Uveal Melanoma: Results From a Single-Arm Phase II Study. *J Clin Oncol.* 2021;39(6):599–607. https://doi.org/10.1200/JCO.20.00605.
48. Middleton MR, McAlpine C, Woodcock VK, Corrie P, Infante JR, Steven NM, et al. Tebentafusp, A TCR/Anti-CD3 Bispecific Fusion Protein Targeting gp100, Potently Activated Antitumor Immune Responses in Patients with Metastatic Melanoma. *Clin Cancer Res.* 2020;26(22):5869–78. https://doi.org/10.1158/1078-0432.CCR-20-1247.
49. Richtig E, Langmann G, Schlemmer G, Müllner K, Papaefthymiou G, Bergthaler P, et al. Verträglichkeit und Wirksamkeit einer adjuvanten Interferon-alfa-2b-Behandlung beim Aderhautmelanom [Safety and efficacy of interferon alfa-2b in the adjuvant treatment of uveal melanoma]. *Ophthalmologe.* 2006;103(6):506–11. https://doi.org/10.1007/s00347-006-1350-7.

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