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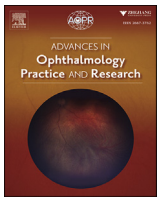

Review

Personalized treatment approaches in intraocular cancer

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ABSTRACT

Background: Intraocular malignant tumors represent a severe disease that threatens vision as well as life. To better extend the life of the patient, preserve visual function, and maintain ocular aesthetics, selecting the appropriate timing and methods of treatment becomes crucial.

Main text: With the continuous advancement of medical technology, the techniques and methods for treating intraocular malignant tumors are constantly evolving. While surgery was once considered the optimal method to prolong patient survival and prevent local recurrence, the discovery and application of various treatments such as radiotherapy, laser therapy, chemotherapy, cryotherapy, and monoclonal antibodies have led to a greater diversity of treatment options. This diversity offers more possibilities to develop personalized treatment plans, and thereby maximize patient benefit. This article reviews the various treatment methods for intraocular malignant tumors, including indications for treatment, outcomes, and potential complications.

Conclusions: Differentiating small intraocular malignant tumors from pigmented lesions is challenging, and ongoing monitoring with regular follow-up is required. Small to medium-sized tumors can be treated with radiotherapy combined with transpupillary thermotherapy. Depending on the tumor's distance from the optic disc, surgery with partial resection may be considered for distant tumors, while proximal tumors may require complete enucleation. Systemic chemotherapy has been widely applied to patients with retinal tumors, lymphomas, and intraocular metastatic cancers, but has limited efficacy in patients with choroidal melanoma. Antagonists of Vascular Endothelial Growth Factor (Anti-VEGF) drugs can improve patient vision and quality of life, while the efficacy of immunotherapy and molecular targeted therapy is still under research.

1. Introduction

Malignant intraocular tumors are classified as primary and secondary and can have a significant impact on vision and life.[1] Primary intraocular tumors are rare and occur primarily in the choroid and retina.[2] In contrast, secondary intraocular tumors have a higher incidence, and occur primarily in the choroid, with the majority located in the posterior uvea.[3] Common primary sites include the breast and lung.[4,5] Retinoblastoma (RB), the most common primary intraocular tumor in children worldwide, is an invasive ocular cancer with approximately 9000 new diagnoses annually worldwide.[6] Choroidal melanoma is the most common primary intraocular tumor in adults, with risk factors including fair skin and light-colored eyes, with an annual incidence of approximately 6 cases per million people in Europe and America.[7,8] Primary intraocular lymphoma is extremely rare and is mainly of B-cell origin, usually limited to the iris, ciliary body, and surrounding choroid.[9,10] (Table 1, Fig. 1).

The goal of managing choroidal melanoma today is to preserve the eye and maintain vision while preventing metastasis as much as possible.[2] Enucleation surgery is gradually being replaced by various forms of radiotherapy, laser therapy, and local tumor excision, often in combination.[11] For retinoblastoma, the chances of survival and vision preservation are usually related to the severity of the disease, emphasizing the critical importance of early detection and diagnosis. Enucleation and intravenous chemotherapy often save a child's life and, in some cases, preserve some vision. [1]Although primary intraocular lymphoma is rare, its incidence is rising annually with the increasing population of immunocompromised individuals. Diagnosis is challenging because the clinical presentation often resembles infectious or non-infectious uveitis

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Table 1
Treatment approaches of intraocular cancer.

Treatment Approaches			Indications	Tumor size	Complications
Surgery	Local Resection	Iris resection and iris ring resection	Iris and ciliary body melanomas	Small, middle	Postoperative hemorrhage, vitreous hemorrhage, retinal detachment, tumor recurrence
		Scleral resection	Smaller tumors without epithelial cells and located away from the posterior globe	Small, middle	
		Endoresection	Patient has poor vision in the other eye and preservation of the eye is crucial	Small, middle	
	Enucleation		Eyes with large tumors, diffuse iris melanomas, painful or blind eye	Small, middle, large	Infection, hemorrhage, wound dehiscence, contraction of the fornices, exposure of the implant
Radiotherapy	Proton Beam		Tumors surrounding the optic disk and fovea; an attempt at eye-sparing treatment	Middle, Large	Second primary tumors, dry eye syndrome, cataracts, radiation retinopathy, optic neuropathy, vitreous hemorrhage
	Brachytherapy		Majority of uveal melanomas (also with limited extrascleral extension)	Small, middle	Cataract, scleral necrosis, neovascular glaucoma, radiation maculopathy, vitreous hemorrhage, dry eye syndrome
	stereotactic	Gamma Knife	Rapidly growing tumors, large tumors, or tumors in an unfavorable location	Middle, Large	Cataract, radiation retinopathy, optic neuropathy, vitreous hemorrhage
Laser	Laser Photocoagulation		Tumors located away from the posterior globe	Small, middle	Hemorrhage, damage to the macula, choroidal detachment, and retinal detachment
	Transpupillary Thermotherapy (TTT)		Small melanomas and retinoblastomas	Small, middle	Hemorrhage, retinal detachment, and blockage of blood vessels in the eye
	Photodynamic Therapy (PDT)		Small choroidal melanomas, especially in cases without pigment deposition	Small, middle	Optic neuropathy, macular degeneration, cataracts, neovascular glaucoma, subretinal exudates, and exudative retinal detachment
Chemotherapy	Systemic Chemotherapy		Bilateral retinoblastoma	Small, middle	Transient alopecia, hematologic reduction, local tissue necrosis, venous inflammation, and fever
	Targeted Chemotherapy	Intra-Arterial Chemotherapy (IAC)	Unilateral retinoblastoma	Small, middle	Optic nerve swelling, retinal detachment, hemorrhage, spasm of the ocular artery
		Intravitreal Chemotherapy (IViC)	Vitreous metastatic carcinoma		Inflammation, vitreous hemorrhage, retinal detachment, cataract
Cryotherapy			Small tumors and seeded lesions located in the sub-retinal or pre-retinal area	Small, middle	Vitreous hemorrhage, subretinal fluid and scarring

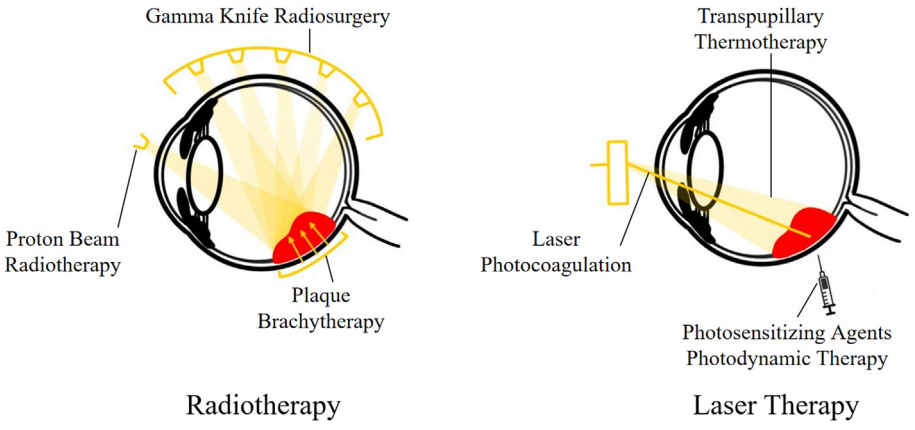

Fig. 1. Schematic figure of Radiotherapy and Laser Therapy.

or other intraocular tumors.[9] Treatment methods differ from other intraocular tumors and mostly involve systemic chemotherapy and intravitreal injection of monoclonal antibodies and chemotherapeutic agents. Despite the potential for tumor control with these newer therapies, the prognosis remains poor.[9,12] Metastatic carcinomas frequently occur in the choroid, and rarely in the retina. Symptoms in most cases result from the continuous growth of the tumor and neovascular glaucoma, leading to pain and blindness.[5] Treatment of ocular metastases is similar to that of choroidal melanoma and includes local radiotherapy and laser therapy to reduce tumor size. Local scleral excision is rarely used, while vitrectomy proves beneficial in improving visual acuity for patients with vitreous metastasis. Enucleation is often reserved for alleviating ocular pain and managing growing tumors.[5,13]

2. Diagnosis

To ensure the maximum quality of life for patients, including the preservation of the eye and vision, beyond determining the tumor type, identifying the location and size of the tumor is crucial for selecting treatment modalities and its outcomes. Given the prevailing understanding that systemic metastasis may occur early in tumor discovery, regular observation and follow-up are the base of a personalized

treatment approach to the patient. This article aims to discuss the evolving techniques and methods for treating intraocular malignant tumors, including their indications, outcomes, and potential complications while highlighting the importance of personalized treatment plans and the challenges in managing them.

Differentiating a small uveal melanoma from a nevus is challenging, often requiring observation over time to detect any growth indicative of melanoma. Key clinical indicators include the presence of orange pigment on the tumor's surface, subretinal fluid accumulation, a tumor thickness exceeding 2 mm, and low internal reflectivity noted during ultrasound examinations (B-Scan).[14] Ancillary tests such as fluorescein angiography and ultrasonography play a crucial role in confirming the diagnosis, with studies showing a gradual increase in the progression rate of choroidal nevi to melanoma over time.[11] Therefore, regular monitoring of nevus is essential for the early detection of malignant lesions.

The process of diagnosing retinoblastoma involves a sequence of diagnostic procedures. Initially, an ophthalmologist assesses the eye for symptoms like whitish pupils, enlarged pupils, crossed eyes, red and painful eyes, and poor vision, using ultrasound to detect abnormalities within the eye.[6] For details, MRI or CT scans may be advised, especially for high-risk cases or post-radiation therapy monitoring.[15] Genetic tests can identify chromosome 13 mutations linked to retinoblastoma, aiding in the diagnostic and treatment planning process.[16,17] Additional assessments such as lumbar puncture or bone marrow biopsy might be conducted to evaluate metastatic involvement.[18]

Vitreoretinal lymphoma, primarily known as intraocular lymphoma, stands as the most prevalent type of eye-related lymphoproliferative disorder. It is specifically characterized by its vitreous and retinal manifestations, distinguishing it from uveal lymphoma, which is subdivided into choroidal, iris, and ciliary body.[19] Patients with vitreoretinal lymphoma often present with symptoms such as blurred vision and floaters, with the disease manifesting as vitreous inflammation or subretinal lesions that resemble leopard pigmentation due to their brown centers and yellow periphery.[20] Diagnosis challenges arise due to its rarity and symptom overlap with other uveal diseases, necessitating evaluations including fluorescein angiography for vascular leakage and optical coherence tomography to monitor subretinal changes.[21,22] The gold standard for diagnosis involves cytopathologic examination of ocular fluids or biopsies, with additional molecular and cytokine analyses aiding in confirmation.[21]

Uveal lymphoma, a rare ocular condition often presents with recurrent, painless episodes of blurred vision and metamorphopsia due to secondary serous retinal detachment. The majority of uveal lymphomas are confined to the choroid while reports of iris and ciliary body involvement have rarely been documented.[23] Choroid lymphoma is characterized by multifocal, yellow choroidal swellings visible on fundus examination, resembling conditions like multifocal choroiditis.[24] Iris and ciliary body lymphoma often present symptoms resembling anterior uveitis, leading to frequent misdiagnoses, relying on tissue sampling or aqueous cytology to identify characteristic lymphoma cells.[10] The use of B-scan ultrasonography is critical in diagnosing this condition, particularly for identifying extra-scleral extension of the choroidal mass. Biopsy remains the definitive diagnostic tool, with immunocytology helping to identify the B-cell origin of most uveal lymphomas. Management requires a comprehensive approach, including neuroimaging to assess for intracerebral disease.[25]

The metastatic disease often affects the eye, particularly the uveal tract, by hematogenous dissemination, with the peripapillary choroid being a common site due to its rich vascular supply.[26] Patients may present with symptoms similar to chronic anterior uveitis or elevated intraocular pressure due to iris neovascularization.[27] Iris and ciliary body metastases may present as nodules.[25] Choroidal metastases usually present with a large amount of subretinal fluid that may lead to retinal detachment, which can be detected by ocular ultrasonography.[25] Due to changes in the retinal pigment epithelium, these metastases tend to have a pale appearance with characteristic leopard pigmentation.[28] The diagnosis of metastatic eye disease particularly requires investigation of the history of cancer in patients with it. Common primary cancers include breast and lung cancer. Imaging techniques such as fluorescein angiography and B-scan ocular ultrasonography with Doppler are crucial to show the features of metastatic tumors, respectively.[29] MRI of the brain may also be performed to check for intracerebral involvement. The rapid growth of ocular lesions is a distinctive hallmark of metastatic disease and may distinguish it from slower-growing primary ocular tumors such as melanoma.[25]

3. Treatment approaches

Tumors on the choroid and iris are challenging to differentiate from pigmented nevi when they are small. Hence, close observation of tumor changes is essential. Appropriate intervention should be performed when necessary to minimize the risk of metastasis and to improve the preservation of the patient's visual acuity. Typically, anterior segment tumors involving the iris and ciliary body are evaluated by ultrasound biomicroscopy (UBM), while posterior segment tumors are evaluated by B-scan ultrasonography. Continuous monitoring aids in assessing the tumor's response to treatment.[30] Color fundus photography, optical coherence tomography (OCT), and fluorescein angiography are also helpful in determining the location and size of the tumor.[31] The 5-year transformation rate for iris pigmented nevi is 2%, increasing to 8% at ten years. Risk factors can be summarized using the acronym ABCDEF, where A (age), B (blood), C (clock hour inferior), D (diffuse), E (ectropion), and F (feathery margin).[32] Choroidal nevi can be detected in 6% of white people, with a transformation rate increasing with age. In the absence of risk factors, the 5-year transformation rate is 3%, but with two or more risk factors, the rate exceeds 50%. These risk factors include thickness, fluid, symptoms, orange pigment, margin, ultrasonographic hollowness, halo absence, and drusen absence.[33]

3.1. Surgical treatment

3.1.1. Local resection

For iris and ciliary body melanomas, the preferred approaches include iris resection and iris ring resection.[34–36] For smaller tumors without epithelial cells and located away from the posterior globe, transscleral local resection can be performed by cutting out the tumor through a scleral opening.[37] Scleral resection is a full-thickness excision procedure involving the sclera, tumor, choroid, and retina. Typically, the scleral resection extends approximately 3 mm beyond the melanoma. Compared to previous techniques, lamellar scleral resection has a less invasive impact on the retina, but it carries a significantly higher risk of tumor recurrence.[38] Postoperative complications include vitreous hemorrhage, retinal detachment, neovascular glaucoma, and tumor recurrence. Surgical success is also influenced by the patient's overall health, as intraoperative bleeding is controlled by lowering the patient's blood pressure (40–50 mmHg) and cauterizing veins in the sclera during the hypotensive phase. Additionally, due to efforts to protect the retina near the tumor during surgery, postoperative radiotherapy is required to prevent tumor recurrence.[39] For tumors thicker than 6 mm, local resection is more effective than radiotherapy.[40] Tumors located in the posterior globe of the choroid are difficult to remove surgically, and the surgical procedure may lead to the spread of tumor cells. Therefore, the preferred options are radiotherapy and enucleation. If the patient has poor vision in the other eye and preservation of the eye is crucial, endoresection can be considered. Endoresection, using vitrectomy for transretinal excision is technically more accessible. However, there is controversy due to concerns about tumor metastasis.[41]

3.1.2. Enucleation

Wardrop was the first to discover that retinoblastoma originates from the retina and can metastasize systemically. He also performed the first enucleation surgery to treat RB.[15] However, due to the imperfect surgical

techniques and the advanced stage of the patient's disease, the procedure failed to save the patient's life. By 1851, with the application of general anesthesia and the use of the ophthalmoscope for eye examination, enucleation became the preferred treatment for RB.[42] In the 1800s, retinoblastoma was a 100% fatal disease, but today, in developed countries, the mortality rate is less than 2%.[7,42] Until half a century ago, enucleation was the only treatment option for RB. However, nowadays, conservative treatments such as radiation therapy, laser therapy, and cryotherapy can be employed to treat patients while preserving functional vision. However in low-income countries, non-surgical options are often challenging to implement, and enucleation remains a crucial treatment method to ensure the patient's survival.[7] After enucleation, a detailed analysis of ocular tissue histopathological characteristics is essential. Histopathological reports provide valuable information for ophthalmic oncologists and could guide the treatment process. If high-risk features are present, including laminar optic nerve invasion, extensive choroidal invasion (diameter >3 mm), or extraocular extension, adjuvant intravenous chemotherapeutic agents may be necessary to prevent metastasis. Conversely, if the ocular pathologist reports the absence of these features, enucleation alone may be curative, and additional chemotherapy may not be required.[43]

Enucleation is the second most commonly performed treatment modality for choroidal melanoma, following radiotherapy. It is recommended for the management of larger tumors (with a diameter exceeding 16 mm or a height exceeding 10 mm), those involving the optic disc, extending beyond one-third of the ciliary body, or exhibiting extensive retinal invasion or perforation. Patients often present with significantly reduced visual acuity at their initial visit.[8] Small tumors (1–5 mm in basal diameter and 0–2.5 mm in apical height) and medium-sized tumors (6–16 mm in basal diameter and 2.5–10 mm in apical height) can also be treated through enucleation. However, Zimmerman and MacLean suggested that enucleation might potentially accelerate tumor metastasis, and for patients aged 65 and above, the survival benefit post-enucleation is not significant.[44,45] However, Singh et al. in their analysis of clinical data published over the past 25 years, contradicted this notion, suggesting that existing evidence indicates a closer relationship between post-treatment mortality and early metastasis of choroidal melanoma.[46] In the Collaborative Ocular Melanoma Study (COMS) clinical trial, Hawkins et al. found that preoperative radiotherapy did not increase the level of postoperative complications compared to the enucleation-only group. Moreover, it was associated with a reduced incidence of postoperative ptosis and secondary tumors.[47]

3.2. Radiotherapy

3.2.1. Proton beam radiotherapy

Proton beam therapy, utilizing charged particles such as protons or helium ions, is a relatively novel conservative treatment method developed in the early 1990s. This approach enables the precise and safe delivery of required energy to the tumor sites with high accuracy and minimal damage to surrounding tissues, such as the optic disc and macula.[30] Proton beam therapy is commonly employed as a conservative alternative for treating unresectable or diffuse iris melanoma, as well as medium or large choroidal melanoma. The treatment is usually divided into multiple sessions, requiring careful positioning of the eyes during the irradiation process. Despite the therapeutic efficacy appearing similar to Brachytherapy, proton beam therapy offers a more uniform and concentrated treatment, resulting in less damage to surrounding tissues. Nevertheless, radiation-related complications can still occur promptly in approximately 50% of cases.[48] Similar to Brachytherapy, most tumors cease growth or regress after treatment. The survival rate following charged particle irradiation is comparable to that after enucleation surgery.[49] Complications may include dry eye syndrome, cataracts, radiation retinopathy, optic neuropathy, vitreous hemorrhage, and neovascular glaucoma. The most severe side effect is the subsequent development of second primary tumors within the radiation field, especially in patients with familial retinoblastoma.[50]

3.2.2. Brachytherapy

Brachytherapy, also known as Plaque Radiotherapy, involves the temporary suturing of radioactive plaques onto the sclera near the tumor, constituting a conservative treatment approach for controlling medium-sized posterior uveal melanomas, which has been one of the oldest, most effective, and widely adopted methods.[51,52] It is also effective in the treatment of iris melanomas, albeit with significantly higher rates of cataract formation and eyelid scar formation compared to External Beam Radiation Therapy (EBRT).[51] Plaque therapy is convenient as it requires only 2–4 days to deliver a full dose, but a drawback is the need for two surgeries for plaque placement and removal. The small size and precision of the plaques make them suitable for smaller tumors, particularly in patients with preserved vision. Ruthenium-106 is the most frequently used in Europe, while Iodine-125 is preferred in the United States. The use of Cobalt-60, Palladium-103, and Strontium-90 is less common. For retinoblastoma patients, brachytherapy is commonly employed as a secondary treatment for medium-sized (maximum basal diameter ≤16 mm, thickness 3–9 mm) chemotherapy-resistant tumors.[42] Despite plaque therapy being very effective in controlling tumors, potential side effects may occur, including cataract formation, scleral necrosis, neovascular glaucoma, radiation maculopathy, and vitreous hemorrhage as well as dry eye syndrome. It has been reported that the success rate of plaque therapy as a secondary treatment after intra-arterial chemotherapy for retinoblastoma is 79%, even in the presence of local vitreous seeding.[53]

3.2.3. Stereotactic radiotherapy

In stereotactic radiotherapy, radiation is delivered to the tumor from multiple directions with a limited number of sessions. The technique involves directing radiation beams from multiple angles to provide a high dose to the tumor while sparing surrounding tissues.[54] Employing multiple precisely focused radiation beams in a limited number of sessions enables high-dose radiation therapy for the ablation of small volumes. This approach maximizes local control while preserving critical adjacent normal tissues. This technology proves effective, particularly for larger tumors or those situated near the optic disc where plaque radiotherapy is impracticable.[55]

Gamma Knife Radiosurgery (GKS) has demonstrated efficacy in treating various ocular conditions, offering high radiation doses and submillimeter accuracy for small to medium-sized targets within the brain.[56] Compared to plaque brachytherapy, GKS presents advantages such as avoiding general anesthesia, same-day treatment, no hospitalization requirement, and absence of extraocular muscle disinsertion. Additionally, GKS can address lesions adjacent to the optic disc. Preliminary data suggest GKS as a potential alternative treatment for uveal melanoma.[57] A recent systematic review and meta-analysis indicated that Gamma Knife radiosurgery emerged as the primary treatment choice for uveal melanoma, demonstrating effective tumor control in 94%–97% of cases and a 5-year survival rate of 76%. Nevertheless, further comparative randomized studies are necessary to assess the position of this technology within the current treatment modalities.[56] The use of GKS and stereotactic radiotherapy in the clinical setting remains controversial and therefore strict clinical guidelines must be adhered to in its use.

3.3. Laser therapy

3.3.1. Laser photocoagulation

Laser photocoagulation, the most used form of laser treatment, involves xenon arc, argon laser, and krypton laser. The principle is to treat tumors in the posterior segment, away from the optic disc, by destroying tumor blood vessels through brief irradiation. Complications include hemorrhage, damage to the macula, choroidal detachment, and retinal detachment.[55] Treatment outcomes vary. Laser photocoagulation is also employed in conjunction with radiotherapy to reduce exudative retinal

detachment associated with uveal melanoma. However, much of the energy from argon lasers is absorbed by the retinal pigment epithelium, with limited energy reaching the choroid. In contrast, infrared lasers used in transpupillary thermotherapy exhibit greater penetration and fewer complications.[58]

3.3.2. Transpupillary thermotherapy (TTT)

Transpupillary thermotherapy employs a high penetration to target uveal melanomas. The wavelength used gradually increases the temperature to kill melanoma cells. In comparison to normal tissue, elevated heat preferentially affects tumor tissue due to the inefficient vascular channels in tumors. This induces cytotoxic damage to the tumor itself, inhibiting the DNA repair mechanisms within cells, rendering the tumor more sensitive to therapeutic interventions such as radiotherapy or chemotherapy, thereby enhancing their efficacy.[59]TTT is applied for smaller melanomas and retinoblastomas, proving effective for small choroidal metastatic tumors as well. An existing challenge is the risk of melanoma cell invasion into the sclera that has not been surgically disrupted. Melanoma cell invasion into the sclera is observed in over 50% of medium and large tumors, Additionally, TTT is less favorable for tumors with a thickness exceeding 4 mm. Complications may include macular edema, retinal vein occlusion, vitreoretinal snow banking, and neovascular glaucoma.[45]

For retinoblastoma, transpupillary thermotherapy using a diode laser has largely replaced laser photocoagulation. Similar to cryotherapy, TTT can be used in conjunction with chemotherapy, serving as a primary treatment for small tumors with a diameter of less than 3 mm and a thickness of less than 2 mm. TTT is typically performed through an indirect ophthalmoscope, requiring multiple spots to cover the entire tumor. The objective is to provide sufficient application time to achieve a grayish-white absorption. TTT treatments are usually repeated every 4 weeks, ranging from 2 to 6 sessions, until achieving a flat scar or complete calcification of the tumor.[60] Complications associated with TTT include iris atrophy, anterior or posterior ciliary body protrusion, and focal cataracts. When appropriately applied, more severe complications endangering vision are rare, including retinal vein occlusion, vitreous hemorrhage, retinal neovascularization, vitreoretinal traction, and retinal detachment.[59]

3.3.3. Photodynamic therapy (PDT)

Recently, PDT has been explored as a treatment option for uveal melanoma cases that have previously failed conventional therapies. PDT is a laser therapy targeting abnormal capillaries, suitable for treating intraocular neovascularization and tumors.[61] The procedure involves intravenous administration of photosensitizing agents, followed by the targeted application of low-power and long-duration infrared laser beams.[62] PDT employs a specific wavelength of laser to irradiate the lesion, activating the photosensitizer. This process generates free radicals or highly reactive singlet oxygen through the venous circulation, leading to cellular lysis and death without causing harm to normal tissues.[63] Preliminary research on photodynamic therapy for choroidal melanoma shows promising results, with favorable prognostic factors being smaller size and lack of pigment deposition. An overall response rate of 80% suggests that PDT may be an effective primary treatment for small choroidal melanomas, especially in cases without pigment deposition.[64]Complications include optic neuropathy, macular degeneration, cataracts, neovascular glaucoma, subretinal exudates, and exudative retinal detachment. When used in conjunction with systemic chemotherapy, immunotherapy, or hormone therapy, PDT emerges as the preferred approach for treating patients with bilateral multifocal choroidal metastases.[64] The retina and optic nerve can only tolerate a limited amount of radiation energy. Excessive exposure can lead to secondary radiation-induced maculopathy and significant post-treatment vision loss. Therefore, controlling radiation dosage during treatment is crucial. Selecting this treatment approach necessitates strict adherence to indications and careful monitoring of radiation energy.[65]

3.4. Chemotherapy

3.4.1. Systemic chemotherapy

Since 1990, systemic chemotherapy has evolved beyond its initial application for treating extraocular tumors and metastases. It is now employed to reduce tumor volume in preparation for subsequent localized treatment, remaining a crucial tool in retinoblastoma therapy. Intravenous chemotherapy (IVC) typically consists of more than 2 types of chemotherapeutic agents administered monthly through central or peripheral catheters, spanning a total of 6–9 cycles. The most used regimen includes three drugs: vincristine, etoposide, and carboplatin. Given the reduction in tumor size, IVC is sometimes referred to as “chemo reduction".[66] Current indications for IVC include bilateral RB, confirmed lineage mutations, a family history of retinoblastoma, or suspected infiltration of the optic nerve or choroid. Similar to most systemic chemotherapy approaches, complications may include transient alopecia, hematologic reduction, local tissue necrosis, venous inflammation, and fever. Chemical immunotherapy has limited efficacy against uveal melanoma due to the immune-privileged nature of the eye, the overall outcomes of systemic chemotherapy are suboptimal.[67] Similarly, primary vitreoretinal lymphoma requires aggressive chemotherapy and radiotherapy, although it typically responds well to initial treatment, the prognosis is generally poor due to a high recurrence rate.[68]

3.4.2. Targeted chemotherapy

3.4.2.1. Intra-arterial chemotherapy (IAC). Intra-arterial chemotherapy is a complex and typically costly procedure conducted under general anesthesia, utilizing microcatheters guided by fluoroscopy to selectively deliver chemotherapeutic agents into the ophthalmic artery.[69] In comparison to IVC, IAC provides a 10-fold increase in the direct delivery of chemotherapy to the eye, making it a preferable option for unilateral retinoblastoma patients.[70] Comparative studies have demonstrated significantly higher efficacy in tumor control with IAC.[71] Although IAC has replaced IVC as the preferred choice in many treatment centers, its adoption is often challenging in low-income countries due to its technical complexity.

3.4.2.2. Intravitreal chemotherapy (IViC). Vitreoretinal lymphoma in one eye can be treated with intravitreal chemotherapy (methotrexate and rituximab) with local therapy.[12] Concerns regarding extraocular tumor seeding and subsequent metastatic spread in retinoblastoma have prompted the development of intravitreal chemotherapy.[72] This technique involves the direct injection of chemotherapeutic agents into the vitreous cavity, resulting in the successful treatment of disseminated tumors within the vitreous at high concentrations.[73]

3.5. Cryotherapy

Cryotherapy remains a reliable and frequently utilized therapeutic modality in the treatment of retinoblastoma.[74] Indications include the treatment of small tumors and seeded lesions located in the sub-retinal or pre-retinal area. It is particularly effective in treating small tumors in the pre-equatorial region and metastatic lesions near the serosa and is the treatment of choice. By reducing the tumor temperature, leading to protein denaturation, cryotherapy disrupts the endothelial cells of the tumor's blood vessels, resulting in ischemic necrosis.[75] Currently, cryotherapy is seldom employed as a standalone treatment; it is more commonly used in combination with a form of chemotherapy, most commonly intravenous chemotherapy, but occasionally intra-arterial chemotherapy.[60] Following extensive cryotherapy, exudative and rhegmatogenous retinal detachments may occur.[76]

3.6. Anti-VEGF monoclonal antibody therapy

Vascular Endothelial Growth Factor (VEGF) is considered a crucial factor in promoting pathological or physiological angiogenesis. Bevacizumab is a recombinant humanized anti-VEGF monoclonal antibody fragment, with relatively minimal clinical side effects.[77] Intravitreal injection of bevacizumab has been proven to be a safe, effective, and relatively straightforward treatment method for choroidal metastases from breast and lung cancers. It functions by reducing the generation of new blood vessels at the fundus, preventing vision loss, and improving the quality of life for patients with these tumors. This approach has been successfully applied to isolated lesions with a thickness of less than 3.5 mm and minimal subretinal fluid.[78] In the study by Fenicia et al. all four cases of choroidal metastatic carcinoma patients treated with intravitreal bevacizumab showed improved visual symptoms, tumor regression, and resolution of serous retinal detachment. However, there is currently no evidence proving that bevacizumab can counteract tumor proliferation and metastasis.[79]

3.7. Targeted therapy and immunotherapy

Molecular targeted therapy appears to be a suitable approach for uveal melanoma, as protein kinase C(PKC) and mitogen-activated protein kinase (MAPK) pathways play a crucial role in its pathogenesis.[80] Clinical trials focusing on PKC or MEK have demonstrated modest activity.[81,82] Unfortunately, inhibitors of the MAPK pathway, either used alone or in combination with chemotherapy, have not shown significant efficacy in clinical trials.[79]

Despite the shared origin of uveal melanoma and cutaneous melanoma, their genetic characteristics seldom overlap, and the mutational burden in uveal melanoma is lower. Up to 50% of uveal melanoma patients experience metastasis, primarily in the liver, with these patients having a poor prognosis and a median overall survival of about 1 year.[83] Consequently, many therapies proven effective for cutaneous melanoma, such as immunotherapy, exhibit minimal effectiveness in uveal melanoma.[84] However, tebentafusp is a bispecific protein that combines an enhanced T-cell receptor with an anti-CD3 effector, redirecting T cells to target cells positive for glycoprotein 100. In a phase 3 trial for metastatic uveal melanoma, tebentafusp significantly improved 1-year overall survival to 73% compared to 59% in the control group, with the most common side effects being cytokine-mediated rash (83%), pyrexia (76%), and pruritus (69%).[85]

4. Conclusions

In summary, the goal of treating intraocular malignancies is to preserve effective vision as much as possible and prevent tumor metastasis that threatens the patient's life. For smaller or suspicious tumors, regular follow-up is necessary. If there is a noticeable growth trend, TTT or external beam radiotherapy combined with TTT may be considered. Radiotherapy is the most commonly used method for medium and small choroidal melanomas, and complications such as cataracts caused by radiotherapy are usually manageable. Larger choroidal melanomas often require enucleation surgery combined with radiotherapy. Local excision is an option for tumors located far from the optic disc. Systemic chemotherapy is employed to alleviate metastases, especially in cases of primary breast cancer. Both laser therapy and radiotherapy are suitable for most intraocular tumors and can achieve satisfactory results. Chemotherapy increases the possibility of preserving the eye and vision for retinoblastoma patients, but in developing countries, enucleation surgery remains a crucial means of protecting patients' lives. Intravitreal injection of anti-VEGF agents serves as palliative treatment, improving neovascularization in the fundus and enhancing visual acuity and quality of life for patients. A comprehensive consideration of the patient's condition is required to select a treatment regimen with better efficacy, lower recurrence rates, fewer adverse reactions, and more effectively improves the patient's vision and quality of life.

Study approval

Not Applicable.

Author contributions

The authors confirm contribution to the paper as follows: Conception and design of study: YK, WF, LH; Manuscript preparation: YL, AR, YG; Manuscript revision: KY, WF, LH; All authors reviewed the results and approved the final version of the manuscript.

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Abbreviations

Anti-VEGF	antagonists of Vascular Endothelial Growth Factor
COMS	collaborative ocular melanoma study
EBRT	external beam radiation therapy
GKS	gamma knife radiosurgery
IAC	intra-arterial chemotherapy
IVC	intravenous chemotherapy
IViC	intravitreal chemotherapy
MAPK	mitogen-activated protein kinase
OCT	optical coherence tomography
PDT	photodynamic therapy
PKC	protein kinase C
RB	retinoblastoma
TTT	transpupillary thermotherapy
UBM	ultrasound biomicroscopy
VEGF	vascular endothelial growth factor

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