Guideline

Guidelines for management of uveal melanoma (2025)

Yi Shao[1], Jian-Min Ma[2], Hua-Sheng Yang[3], *Guidelines for management of uveal melanoma (2025), Ophthalmic Imaging and Intelligent Medicine Branch Chinese Medicine Education Association; Ophthalmology Committee of International Association of Translational Medicine; Ophthalmology Committee of International Association of Intelligent Medicine*

[1]Department of Ophthalmology, Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, National Clinical Research Center for Eye Diseases, Shanghai 200080, China

[2]Beijing Tongren Hospital Ophthalmic Center, Capital Medical University, Beijing 100000, China

[3]Zhongshan Ophthalmology Center, Sun Yat sen University, Guangzhou, Guangdong 510060, China

Author Introduction:

Dr. Yi Shao is a Chief Physician, Professor, and MD/PhD who serves as Vice President of the International Society of Translational Medicine and Intelligent Medicine, leading their ophthalmology committees. A Fellow of the Royal Society of Medicine and Bascom Palmer Eye Institute scholar, he ranks among the world's top 2% scientists (2021-2024) and is recognized as a leading global expert in dry eye (19th) and Chinese ophthalmology (Top 100, 15th). Honored as a Young Leading Talent by China's national and provincial authorities, he has published 312 SCI papers, developed 28 guidelines (6 international), established 2 national standards, holds 32 patents, and authored/edited 36 books. Leading 6 national and 12 provincial research projects, he has won 16 provincial awards (6 first prizes) as principal investigator.

Dr. Jian-Min Ma is a postdoctoral fellow, chief physician, and Ph.D. mentor who leads the Ocular Oncology Committee under the Ophthalmology Branch of the Chinese Medical Doctor Association. With extensive expertise in complex ocular tumors and orbital disease management, Dr. Ma has published over 300 articles in journals worldwide. He has contributed to nearly 70 medical books, serving as chief editor for 13 volumes, associate editor for 12, and co-author of 10 ophthalmology textbooks used in medical education. Additionally, he has collaborated as a principal investigator on six national research projects, including five funded by the National Natural Science Foundation, along with over ten municipal projects. His work has earned him more than 30 professional awards.

Dr. Hua-Sheng Yang, Ph.D., Chief Physician, Supervisor for Doctoral Candidates, was among the first batch of leading medical talents in Guangdong Province. He serves as the Deputy Director of the Ophthalmic Oncology Committee of the Chinese Medical Doctor Association, and the Deputy Director of the Ophthalmic Oncology Branch of the Chinese Anti-Cancer Association. Dr. Yang is proficient in the diagnosis and treatment of various difficult and complicated ophthalmic tumors and orbital diseases. He has presided over four National Natural Science Foundation projects and published more than 170 papers, over 70 of which were indexed by the SCI. He has received one second-class and one third-class award for scientific and technological progress in Guangdong Province.

Correspondence to: Yi Shao, **email:** freebee99@163.com; Jian-Min Ma, **email:** jmma@sina.com; Hua-Sheng Yang, **email:** Yanghs64@126.com

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ABSTRACT

The guidelines for uveal melanoma have undergone substantial transformations with the introduction of advanced diagnostic and therapeutic technologies. This article aims to elucidate the complex application of contemporary advancements in the management of uveal melanoma, a field that holds significant promise yet presents unique challenges due to its intricate biological behavior. Historically, the therapeutic landscape of uveal melanoma was predominantly characterized by surgical interventions. However, advancements in medical science, particularly the development of immunotherapies and targeted therapies, have shifted this paradigm. When combined with the rapid expansion of genomic and proteomic data, the role of these novel treatments in managing uveal melanoma has been firmly established, transitioning from experimental stages to clinical practice. Acknowledging this transformative potential, collaborations between the Ophthalmic Oncology Subcommittee of the International Ophthalmological Society and the Melanoma Research Consortium have been instrumental. These distinguished organizations convened a panel of experts to examine and integrate the latest advancements from both national and international sources. Their scope extended beyond the implementation of innovative therapies for uveal melanoma, encompassing the identification of existing barriers and the outlining of future directions. Following thorough deliberations, the consensus synthesized in this document serves as a guiding framework for ophthalmologists and oncologists, facilitating the effective incorporation of contemporary advancements into treatment strategies and the advancement of clinical research. This guideline aims to provide a comprehensive framework, ensuring that clinical decisions are not only informed but transformed by the latest scientific developments. By building upon existing knowledge while adhering to the highest standards of originality, this document exemplifies both innovation and scholarly integrity, aligning with the principles of esteemed journals such as Ophthalmology and Cancer Research.

INTRODUCTION

Uveal melanoma (UM) is the most common primary malignant intraocular tumor in adults, significantly threatening the life and visual function of affected individuals. It constitutes approximately 79% to 81% of ocular melanomas and 3% to 5% of all melanoma cases [1]. UM originates from melanocytes located within the uveal tract, which includes the iris, ciliary body, and choroid. Approximately 90% of UM cases occur in the choroid, while the remaining 10% are found in the iris and ciliary body, typically presenting as monocular [2]. The global incidence rate of uveal melanoma ranges from 0.0001% to 0.0009% [3], with significant geographic and racial disparities. The highest prevalence is observed among Caucasians, followed by Asians, with a lower incidence in individuals of African descent. Additionally, the prevalence

is slightly higher in males compared to females. Approximately 50% of patients with UM eventually develop hematogenous metastasis, predominantly affecting the liver. A study conducted at Wills Eye Hospital in the United States reported that the 5-, 10-, and 15-year metastasis rates for large UM tumors were 35%, 49%, and 67%, respectively, while the rates for medium-sized tumors were 14%, 26%, and 37% [4, 5]. A long-term follow-up study of 1,553 Chinese UM patients at Beijing Tongren Hospital of Capital Medical University revealed 5-, 10-, and 15-year metastasis rates of 19%, 27%, and 31%, respectively. Additionally, the Eye, Ear, Nose and Throat Hospital of Fudan University documented 5- and 10-year metastasis rates of 20% and 30% for UM, respectively [6]. The age at initial diagnosis for most international patients ranges from 50 to 70 years [7], whereas Chinese patients are typically diagnosed at a younger age, with an average of approximately 45 years [8].

In recent years, advancements in diagnostic and therapeutic methodologies have significantly improved the local control rate of UM. Nevertheless, these advancements have not translated into a corresponding increase in survival rates, as UM continues to exhibit high rates of metastasis, morbidity, and mortality [1,4,8]. The liver (89%), lungs (29%), and bones (17%) are the most common sites for metastasis [1]. Importantly, the median survival time for patients with metastatic UM is only 6 to 12 months [9].

To standardize the clinical diagnosis and treatment of UM, the Ophthalmology Committee of the China Medical Education Association, the Oculoplastic and Orbital Disease Group of the Ophthalmology Branch of the Chinese Medical Association, and the Ocular Tumor Committee of the Chinese Anti-Cancer Association convened a panel of domestic experts specializing in fundoplication, ocular tumors, ocular pathology, radiation therapy, and interventional therapy. These experts engaged in comprehensive discussions and developed a consensus statement on the diagnosis and treatment of UM. This consensus, informed by both domestic and international literature and tailored to the specific context of the country, serves as a reference for clinicians in ophthalmology and related fields.

PATHOGENESIS

Despite the high metastatic potential of UM, metastatic lesions are detectable in fewer than 4% of patients at the time of initial diagnosis [10]. It is likely that most patients have clinically undetectable micrometastases at diagnosis, which supports the classification of UM as a systemic disease [11]. The pathogenesis of UM is intricately linked to molecular genetics, epigenetics, cellular immunity, and environmental factors. Chromosomal abnormalities in UM cells include deletions of chromosome 3 and amplifications of the long arms of chromosomes 6 and 8. Monosomy of chromosome 3 is the most common karyotypic aberration, occurring in approximately 50% to 60% of patients [12]. The deletion of chromosome 3 is a prognostic indicator for the increased likelihood of metastasis in UM [13]. Additionally, chromosome 3 deletion is associated with a higher propensity for metastasis and a poor prognosis [13]. In contrast, amplification of the long arm of chromosome 6 is frequently observed in patients with low-risk UM, whereas amplification of chromosome 8 correlates with a poor prognosis [14].

The primary oncogenic mutations in UM include gain-of-function mutations in GNAQ or GNA11 [15], deletion of the oncogene histone deubiquitylating enzyme BAP1 [16], and mutation of the splicing factor SF3B1 gene [17]. Notably, gain-of-function mutations in GNAQ and GNA11 are present in 91% of UM patients and are considered critical driver mutations. These mutations activate multiple signaling pathways, including mitogen-activated protein kinase kinase, protein kinase C, and Yes-associated proteins, thereby promoting the malignant transformation of UM [18]. The histone deubiquitinating enzyme BAP1 is a critical oncogene in the pathogenesis of UM, with its deletion occurring in 50% of UM patients. The loss of BAP1 function impairs UM cell adhesion, triggers cytoskeletal remodeling, and facilitates the metastasis of UM cells [19]. Additionally, mutations in the splicing factor SF3B1 gene are detected in approximately 25% of UM patients, leading to the production of aberrant transcription products within the tumor tissue. These abnormal transcription products significantly contribute to tumor proliferation in UM [17].

It is significant to note that certain patients with UM

do not exhibit the typical genetic mutations commonly associated with the disease, yet they experience some of the poorest prognoses. This observation suggests the involvement of additional factors in UM pathogenesis. Recent studies have demonstrated that epigenetic imbalances play a crucial role in the development and progression of UM [20]. For instance, histone H3K27 methylation in UM can inhibit immune antigen presentation, thereby facilitating immune escape [21]. Furthermore, abnormal chromosomal conformations in UM can create oncogenic enhancers, activating the expression of the oncogene NTS and promoting malignant transformation [22]. Additional epigenetic factors, including m6A RNA methylation, histone lactylation, and long non-coding RNAs, are also implicated in UM pathogenesis [23-25]. Importantly, pharmacological interventions targeting these epigenetic abnormalities, such as DNA methyltransferase inhibitors (DNMTi) and histone deacetylase inhibitors (HDACi), have been shown to effectively inhibit the malignant transformation of UM [26-28].

DIAGNOSIS

Symptoms and signs

UM encompasses melanomas located in the iris, ciliary body, and choroid, e. Choroidal melanoma typically manifests with symptoms such as persistent photopsia, scotomas, visual field defects, or vision loss, although some patients may remain asymptomatic. Choroidal melanomas are classified into three morphological types: dome-shaped, mushroom-shaped, and flat diffuse. Dome-shaped choroidal melanomas are restricted to the choroidal stroma and have not breached Bruch's membrane. In contrast, mushroom-shaped choroidal melanomas are bilobed tumors that penetrate Bruch's membrane and extend into the subretinal space. Flat diffuse melanomas exhibit a flat, widespread growth pattern and are often misdiagnosed as choroidal nevi. Choroidal melanoma is characterized by the absence of retinal trophoblastic vessels and frequently leads to exudative retinal detachment, occasionally accompanied by vitreous hemorrhage, which results in visual impairment [29].

Iris melanoma is clinically uncommon and is often discovered incidentally, presenting with changes in iris pigmentation (heterochromia) and pupil distortion [30]. Iris melanomas are categorized into nodular and diffuse types, manifesting as pigmented, non-pigmented, or mixed pigmented tumors. Nodular iris melanomas are characterized by a dome-shaped morphology and the presence of dilated trophoblastic vessels. In contrast, diffuse iris melanomas are marked by increased pigmentation of the iris without the formation of a discernible mass. As the condition advances, iris melanoma can lead to complications such as iris ectasia, anterior chamber hemorrhage, and secondary glaucoma. Further progression may result in tumor seeding within the anterior chamber and potential extraocular dissemination.

Ciliary body melanoma is often obscured by the iris, resulting in minimal early-stage symptoms. Consequently, it is frequently not diagnosed until more pronounced symptoms, such as lens displacement, retinal detachment, or extra-scleral extension, become apparent. Upon pupil dilation, the mass may be visualized posterior to the lens. Additionally, the presence of outer scleral trophoblastic blood vessels, known as anterior sentinel vessels, serves as a significant indicator for the potential presence of melanoma [31].

Ophthalmologic examination

Patients necessitate a thorough evaluation of visual acuity, intraocular pressure, the anterior segment of the eye, and the fundus. The primary ophthalmologic examination techniques include slit lamp microscopy and indirect ophthalmoscopy, with occasional use of gonioscopy or transillumination. All patients underwent assessment using a slit lamp microscope for the anterior segment and an indirect ophthalmoscope for the posterior segment to ascertain the location, shape, pigmentation, vascular distribution, tumor margin morphology, distance from the

macula and optic disc, as well as involvement of the ciliary body and cornea, anterior extrascleral extension, and to identify secondary pathologies such as malignant transformation of a choroidal nevus. This includes anterior sentinel vessels on the scleral surface, cataracts, subretinal fluid, or tumors with orange pigment. Gonioscopy is employed to detect iris or ciliary body melanoma affecting the anterior chamber angle, while transillumination, either transscleral or pupillary, is utilized to determine the extent of ciliary body involvement.

Imaging examination

Photography of the anterior segment of the eye and fundus serves as an objective method to document the distribution, morphology, pigmentation, and presence of trophoblastic vessels in iris and ciliary body tumors, as well as extra-scleral extensions, anterior sentinel vessels of the sclera, and other lesions. It also captures the location and morphology of the lens and pupil. In cases of ciliary body and choroidal melanomas, it is essential to achieve full pupil dilation for thorough examination. Simultaneous recording of the peripheral fundus is crucial to delineate the tumor's location and extent, as well as any associated exudative retinal detachment. Ultra-wide-angle fundus imaging provides a more comprehensive depiction of the choroidal melanoma's size and extent, and its relationship with the macula and optic disc. This imaging modality is particularly advantageous for visualizing multiple scattered choroidal melanomas concurrently and for assessing the extent and severity of combined exudative retinal detachment in relation to the tumor. In contrast, conventional fundus photography offers a clearer and more objective representation of the tumor surface details, including color and pigment distribution. For the assessment of choroidal melanoma, a combination of diagnostic techniques is recommended [32].

Ultrasonography and ultrasound biomicroscopy are pivotal in this regard. Ultrasonography, in particular, is the most prevalent method for determining the volume of choroidal melanoma and plays a vital role in its screening, diagnosis, treatment, and monitoring. On ocular ultrasound A-scan, choroidal melanoma is characterized by moderately low internal reflectivity, with a peak at the tumor's apex and a subsequent gradual decline in reflectivity as the sound waves traverse the mass. Typically, on ultrasound imaging, choroidal melanoma presents as dome-shaped, mushroom-shaped, or flat, often exhibiting a positive scooping sign and involving a choroidal depression. Ultrasonography is instrumental in determining whether a tumor has invaded the orbit. The application of color Doppler flow ultrasound facilitates the differentiation between a solid tumor and a hemorrhage by assessing the blood supply and flow within the lesion. In patients with choroidal melanoma, ultrasonography, when employed alongside conventional methods, allows for dynamic observation of blood perfusion within the tumor. Through post-processing and image analysis, perfusion curves and quantitative diagnostic parameters can be derived [33]. Choroidal melanoma typically exhibits the circulatory metabolic characteristics of malignant tumors, with the ultrasonography time-intensity curve demonstrating a rapid-in-rapid-out pattern [34]. Ultrasound bio-microscopy is frequently utilized to evaluate tumors of the iris and ciliary body. Its high resolution enables detailed visualization of the lesion's internal structure and its potential invasion into surrounding tissues, which is crucial for assessing the volume of ciliary body melanoma, the presence of extrascleral spread, and the extent of iris tumor invasion into the ciliary body (Figure 1).

Orbital magnetic resonance imaging (MRI) offers high resolution and is particularly effective in detecting the spread of extrascleral tumors. It is considered more valuable than computed tomography (CT) in the imaging of UM and its relationship to the orbit, especially in cases involving large tumors. Typical MRI indicators of choroidal melanoma include a mass located posterior to the equator, often presenting as thick, mushroom-shaped, or hemispherical. However, the diagnostic value of the mass's morphology is limited. Characteristically, MRI of UM exhibits a high signal intensity on T1-weighted images (T1WI) and a low signal intensity on T2-weighted images (T2WI), relative to the signal of the brain's gray matter. The majority of UMs demonstrate mild enhancement on contrast-enhanced scans, in contrast to melanocytomas, which do not enhance, and most other tumors, which show moderate to significant enhancement [35]. Clinically, retinal detachment is frequently observed. It is recommended to use the brain's gray matter as a reference

for determining the signal intensity of ocular masses, as it provides higher diagnostic accuracy compared to using the vitreous body as a reference. Although orbital CT is less commonly employed for the diagnostic imaging of UM, it retains value in imaging large tumors and assessing orbital invasion (Figure 2).

Fluorescein fundus angiography (FFA) and indocyanine green angiography (ICGA) are instrumental in the evaluation of choroidal melanoma. In the early stages, FFA typically reveals patchy hyperfluorescence, while in the later stages, diffuse fluorescence leakage may be observed due to continuous leakage from the tumor vasculature. Prior to the tumor breaching Bruch's membrane, ICGA images do not display the choroidal blood vessels within the tumor, attributable to either dense pigmentation or an absence of blood vessels within the tumor. However, once the tumor penetrates Bruch's membrane, ICGA examination reveals retinal macrovessels at the tumor site with varying diameters and disorganized alignments, alongside various abnormal vascular formations within the tumor. Post-radiation therapy, tumors may exhibit pre-retinal or subretinal neovascularization, indicative of radiation retinopathy as a complication of radiation treatment [36].

Optical Coherence Tomography (OCT) is a valuable imaging modality for detecting subtle retinal abnormalities, such as subretinal fluid, intraretinal edema, irregular morphology of the photoreceptor layer, and tumor-induced compression of the choroid. It also facilitates the identification of choroidal defects within tumors, as well as the cross-sectional configuration of choroidal capillaries, orange pigment, and choroidal lesions compressed by tumors. Compared to ultrasonography, OCT offers superior advantages in measuring the thickness of small choroidal melanomas [37]. OCT of the anterior segment of the eye is recommended for examining iris melanomas; however, the basal margin of the tumor may be obscured by pigmentation. Additionally, fundus coherence photomicrographic angiography can be employed to monitor macular microangiopathy following radiation therapy, thereby providing a basis for clinical treatment [38].

Positron emission tomography-computed tomography (PET-CT) scans exhibit high sensitivity and predictive value in monitoring systemic metastases in patients with UM. For individuals with UM metastasis, PET-CT is recommended for the early detection of metastases and accurate tumor staging, which is crucial for effective patient management and follow-up. Furthermore, PET-CT is instrumental in identifying primary foci of choroidal metastatic carcinoma [39].

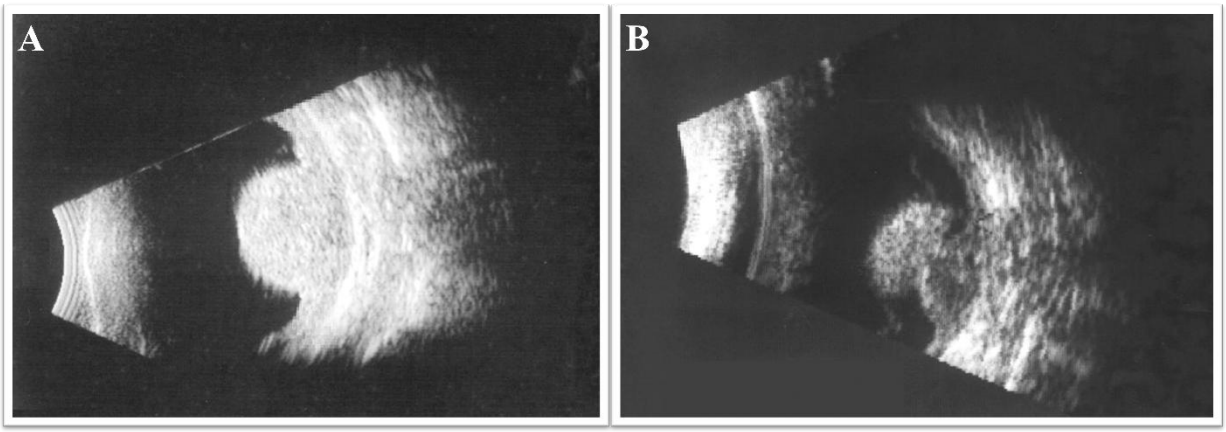

Figure 1: B-scan Ultrasound Images of Choroidal Melanoma. A) The choroidal melanoma demonstrates a mushroom-shaped growth. B) The tumor shows an excavation sign.

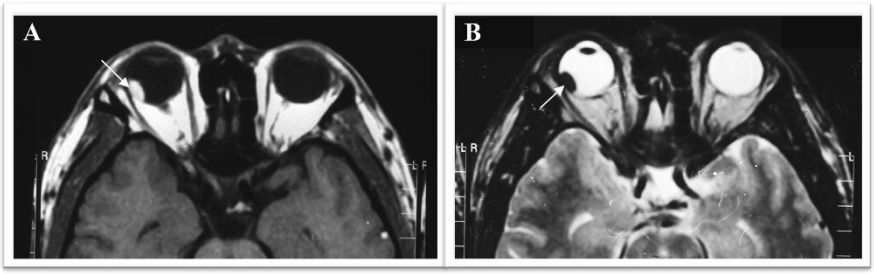

Figure 2: Axial Orbital MRI Images of Choroidal Melanoma. A) High signal on T1WI (arrow). B) Low signal on T2WI (arrow).

Diagnosis and differential diagnosis

A range of lesions present with clinical features similar to those of choroidal melanoma. Common differential diagnoses include optic disc melanocytoma, choroidal melanocytosis, choroidal metastatic carcinoma, retinal pigment epithelial adenoma or adenocarcinoma, choroidal nevus, peripheral exudative hemorrhagic choroidal retinopathy, congenital hypertrophy of the retinal pigment epithelium, hemorrhagic detachment of the retina or pigmented epithelium, choroidal hemangioma, polypoid choroidal lesions, and age-related macular degeneration.

In cases where patients exhibit atypical clinical presentations, diagnostic vitreous surgery and fine-needle aspiration biopsy (FNAB) can provide clarity in diagnosis [40]. For choroidal melanoma biopsy sampling, 25-gauge or 27-gauge diagnostic vitreous surgery is recommended, as it minimizes the risk of hemorrhage and retinal detachment while ensuring adequate sample collection under visual guidance. FNAB, performed via the scleral or transvitreous route, can preserve retinal integrity when executed correctly, with a low incidence of ocular complications. Conducting FNAB prior to initiating therapeutic interventions can enhance treatment safety [41]. Tumor samples obtained through FNAB are valuable for molecular pathology testing, which aids in prognostic assessment in addition to confirming the diagnosis. Nevertheless, FNAB is associated with potential risks, including insufficient sampling, medical injury, and the extraocular spread of tumors; therefore, it should be employed with caution [42].

International staging

UM is primarily staged using two principal systems, both of which are predicated on tumor thickness and basal maximum diameter. The first of these systems was developed by the Collaborative Ocular Melanoma Study (COMS) Group [43], while the second, known as the TNM staging system, was introduced by the American Joint Committee on Cancer (AJCC) in 1968 [44]. In the COMS staging system, tumors are categorized as small (thickness between 1.5 and 2.4 mm and maximum basal diameter between 5 and 16 mm), medium (thickness between 2.5 and 10.0 mm and maximum basal diameter $\leqslant$16 mm), and large (thickness >10.0 mm or maximum basal diameter >16 mm), based on tumor thickness and maximum basal diameter. Conversely, the TNM staging system classifies tumors into stages T1, T2, T3, and T4, where "T" refers to the characteristics of the primary tumor, including its volume and infiltration into surrounding tissues; "N" represents the degree and extent of regional lymph node involvement; and "M" denotes the presence of distant metastasis. There is a partial overlap between small and medium-sized tumors in the COMS staging system and stages T1 and T2 in the TNM staging system, as well as between large tumors in COMS staging and stages T3 and T4 in TNM staging.

In the 8th edition of the TNM staging system, introduced by the AJCC in 2018, a more detailed staging of iris melanomas and the extra-scleral spread of tumors was implemented. Primary tumors are categorized into stages T1 to T4 based on clinical characteristics: stage T1 includes tumors confined to the iris; stage T2 encompasses tumors invading the ciliary body and/or choroid; stage T3 involves tumors invading the ciliary body and/or choroid

with scleral infiltration; and stage T4 includes tumors with extrascleral spread. The 8th edition of the TNM staging system also updated the staging criteria for ciliary body and choroidal melanoma (Table 1).

UM is classified into stage N0, indicating no lymph node involvement, and stage N1, indicating lymph node involvement. Additionally, it is categorized into stage M0, indicating no metastasis, and stage M1, indicating metastasis. The metastatic lesions are further classified into stages M1a to M1c based on their size.

The AJCC evaluates patient prognosis using the TNM staging system, categorizing patients into seven distinct groups based on the assessed prognosis (Table 2).

Table 1. TNM Staging of Primary Tumor Characteristics in Ciliary Body and Choroidal Melanoma, 8th Edition of AJCC.

Primary Tumor Characteristics and Stages (T)		Tumor Characteristics
T1		1. Tumor base diameter between 3.0~9.0 mm, thickness ≤6 mm 2. Tumor base diameter between 9.1~12.0 mm, thickness ≤3 mm
	T1a	T1 tumor without involvement of the ciliary body, no extrascleral extension
	T1b	T1 tumor involving the ciliary body
	T1c	T1 tumor without involvement of the ciliary body, extrascleral extension with maximum diameter ⩽5 mm
	T1d	T1 tumor involving the ciliary body, extrascleral extension with maximum diameter ≤5 mm
T2		1. Tumor base diameter <9.0 mm, thickness between 6.1~9.0 mm 2. Tumor base diameter between 9.112.0 mm, thickness between 3.19.0 mm 3. Tumor base diameter between 12.1~15.0 mm, thickness ≤6.0 mm 4. Tumor base diameter between 15.1~18.0 mm, thickness ≤3.0 mm
	T2a	T2 tumor without involvement of the ciliary body, no extrascleral extension
	T2b	T2 tumor involving the ciliary body
	T2c	T2 tumor without involvement of the ciliary body, extrascleral extension with maximum diameter ≤5 mm
	T2d	T2 tumor involving the ciliary body, extrascleral extension with maximum diameter ≤5 mm
T3		1. Tumor base diameter between 3.1-9.0 mm, thickness between 9.1-12.0 mm 2. Tumor base diameter between 12.1-15.0 mm, thickness between 6.1-15.0 mm 3. Tumor base diameter between 15.1-18.0 mm, thickness between 3.1-12.0 mm
	T3a	T3 tumor without involvement of the ciliary body, no extrascleral extension
	T3b	T3 tumor involving the ciliary body
	T3c	T3 tumor without involvement of the ciliary body, extrascleral extension with maximum diameter ≤5 mm
	T3d	T3 tumor involving the ciliary body, extrascleral extension with maximum diameter ≤5 mm
T4		1. Tumor base diameter between 12.1~15.0 mm, thickness >15.0 mm 2. Tumor base diameter between 15.1~18.0 mm, thickness >12.1 mm

	3. Tumor base diameter >18.0 mm, thickness not limited
T4a	T4 tumor without involvement of the ciliary body, no extrascleral extension
T4b	T4 tumor involving the ciliary body
T4c	T4 tumor without involvement of the ciliary body, extrascleral extension with maximum diameter ≤5 mm
T4d	T4 tumor involving the ciliary body, extrascleral extension with maximum diameter ≤5 mm
T4e	Any tumor size with extrascleral extension with maximum diameter >5 mm

Table 2. TNM Staging Characteristics for Prognostic Classification of Ciliary Body and Choroidal Melanoma by the American Joint Committee on Cancer.

Prognostic Classification		Primary Tumor Characteristics (T)	Lymph Node Involvement (N)	Distant Metastasis (M)
Ⅰ		T1a	N0	M0
Ⅱ	ⅡA	T1b~T1d, T2a	N0	M0
	ⅡB	T2b, T3a	N0	M0
Ⅲ	ⅢA	T2c, T2d, T3b, T3c, T4a	N0	M0
	ⅢB	T3d, T4b, T4c	N0	M0
	ⅢC	T4d, T4e	N0	M0
Ⅳ		Any T	N1	M1a-M1c

TREATMENT

In recent years, significant advancements in the treatment of UM have been achieved, characterized by rapid and multifaceted developments. Commonly utilized therapies include peripapillary radiation therapy and enucleation. Additionally, a variety of eye-preserving treatments are available, such as transpupillary thermotherapy (TTT), particle radiation therapy, stereotactic radiation therapy, and local excision of ocular tumors. The selection of an appropriate UM treatment regimen is contingent upon several factors, including tumor size, location, and associated features like retinal detachment, vitreous hemorrhage, or retinal infiltration (Table 1). Furthermore, the choice of treatment modality must take into account the tumor's volume and location, as well as its associated characteristics. It is also essential to consider the patient's age, overall health, condition of the fellow eye, and personal preferences (Table 3). Principles for developing treatment recommendation levels [45] involve a simplified scoring system designed to distinguish and indicate both the strength of recommendations and the quality of evidence underlying those recommendations. The strength of recommendation is classified into two categories: strong recommendation [Ⅰ] and cautious recommendation [Ⅱ]. A strong recommendation [Ⅰ] is attributed to interventions where the benefits substantially outweigh the adverse effects. In contrast, a cautious recommendation [Ⅱ] is assigned to interventions where the evidence is either of low quality or poorly directed, resulting in an insufficient assessment of benefits versus risks. The quality of evidence is further categorized into four levels.

Level A (high quality), where the evidence is robust and the probability of future research significantly altering the current conclusions is low.

Level B (intermediate quality), where the evidence is moderate and there is a possibility that further research could impact the current conclusions.

Level C (low quality), where the evidence is inadequate and the likelihood of future research significantly affecting the current conclusions is high.

Level D (very low quality): Current consensus among

experts is limited, or there is a paucity of evidence at this juncture.

Table 3. Treatment Methods for UM.

Treatment Method	Indication	Treatment Outcome	Complications	Supplementary Information	Recommendation Grade
			Radiotherapy		
Epiretinal brachytherapy (^{125}I, ^{106}Ru)	Small, medium, and large UM with a basal diameter <20 mm	Good local tumor control	Vision loss; tumor recurrence	Adjust dose to delay vision loss	Ⅰ, A
Plaque brachytherapy	Medium and large UM	Good local tumor control	Vision loss; neovascular glaucoma; tumor recurrence	Not available in all ophthalmic institutions	Ⅱ, B
Stereotactic radiotherapy	UM near the optic disc; unsuitable for brachytherapy or surgery	Good local tumor control	Vision loss; radiation-related complications; tumor recurrence	Not available in all ophthalmic institutions	Ⅱ, C
			Laser treatment		
TTT	Small UM; local recurrence of UM; adjuvant therapy	Improved local tumor control	Vision loss; extraocular tumor recurrence	Occasionally used for small UM nasal to the optic disc	Ⅰ, A
Photodynamic therapy (PDT)	Small UM	Uncertain	Tumor recurrence	Avoids radiotherapy complications; not widely used	Ⅱ, B
			Surgery		
Enucleation or combined with brachytherapy	Medium and large UM with a small basal diameter	Uncertain	Retinal detachment; vision loss; enucleation; tumor recurrence	Rarely combined with brachytherapy; combined to reduce recurrence risk	Ⅱ, B
Intraocular resection or combined with radiotherapy	Medium and large UM; tumor toxicity syndrome	Inconsistent results	Transient intraocular hemorrhage; rare tumor dissemination	Only adopted in some ophthalmic institutions	Ⅱ, B
Enucleation	Large UM; with neovascular glaucoma or extensive retinal detachment	100% local tumor control if completely resected	Socket-related complications; orbital tumor recurrence	Good cosmetic effects with orbital implants and artificial eyes	Ⅰ, A

Exenteration	Extraocular extension of UM	100% local tumor control if completely resected	Orbital tumor recurrence	Rarely used	Ⅱ, B

Abbreviation: UM, uveal Melanoma; TTT, transpupillary thermotherapy.

Patch radiation therapy

Patch radiation therapy, a modality of brachytherapy, is considered the preferred treatment for small to medium-sized tumors, defined as those with a maximum tumor base diameter of ⩽18 mm and a thickness of ⩽10 mm [46]. Commonly utilized radioisotopes inthis treatment include iodine-125 (125I) and ruthenium-106 (106Ru). This technique involves the precise placement of a curved dressing containing radioactive particles on the scleral surface corresponding to the tumor location, allowing radiation to penetrate through the sclera and target the tumor. It is essential that the radiation dose delivered to the tumor apex achieves a range of 80-100 Gy. This therapeutic approach has been shown to effectively control tumor growth while preserving ocular integrity and partial visual function. According to the COMS staging, the five-year survival rate for patients with intermediate-sized tumors following patch radiation therapy (82%) is comparable to that of enucleation alone (81%) [47]. However, the primary complications associated with patch radiation therapy include local radiation-induced neovascular glaucoma, radiation retinopathy, and radiation optic neuropathy, in addition to intraoperative hemorrhage, adjacent tissue injury, and postoperative infection related to the surgical procedure.

TTT

TTT is a non-invasive therapeutic modality that employs an 810 nm infrared diode laser to elevate the temperature of choroidal tumors to between 45 and 60°C. This thermal increase induces vascular occlusion and subsequent tumor necrosis. TTT can penetrate to a maximum depth of 4 mm, making it particularly suitable for small, thick tumors located at the optic disc or outside the macula, especially in cases of primary tumors or local recurrences following complete tumor excision via vitrectomy. It demonstrates enhanced efficacy in treating choroidal melanomas of significant thickness. Tumors exceeding 3 mm in thickness are recommended to be treated with a combination of proton beam radiotherapy (PBRT) and TTT, commonly referred to as "sandwich" therapy. The advantages of TTT include precise laser targeting, immediate induction of tumor necrosis, minimal damage to adjacent healthy choroidal tissue, ease of administration, outpatient treatment feasibility, and the potential for repeated applications. However, TTT is associated with a propensity for tumor recurrence and potential complications, including anterior retinal membrane formation, branch retinal vein occlusion, retinal traction, and secondary retinal detachment at the foramen ovale [48].

PDT

PDT is a non-thermal treatment modality that utilizes a laser-activated photosensitizing dye, specifically vitexoporfin, to induce vascular closure, tumor necrosis, and apoptosis. This approach is applicable in the management of small choroidal melanomas [49]. Nevertheless, the presence of tumor pigmentation can diminish the efficacy of PDT, thereby limiting its application primarily to small, unpigmented choroidal melanomas. Additionally, PDT serves as an adjuvant to radiation therapy and as a complementary treatment following the failure of radiation therapy.

Particle radiation therapy

In contrast to traditional photon radiation therapy, particle radiation therapy is a form of long-distance radiation treatment that employs charged particles, such as protons, carbon ions, and helium ions, as the radiation source. These particle beams are accelerated to high energies using an accelerator and are delivered into the body with precision, concentrating their energy release at the target site. Upon acceleration, the particle beam is precisely directed into the body, where it releases energy at the lesion site, resulting in a sharply attenuated energy distribution known as the Bragg peak. Consequently, particle radiation therapy minimizes damage to surrounding healthy tissues, offers precise targeting, and ensures uniform dose distribution, making it the preferred method for UM radiation therapy [46, 50]. The study results indicate that particle radiation therapy provides superior tumor control compared to photon radiation therapy, although it may be associated with a higher likelihood of anterior foregut complications [51]. Due to its precise targeting capabilities, particle radiation therapy is highly versatile and particularly effective for treating challenging tumors located near the macula or optic disc.

Local excision of tumor

Initially, local excision of tumors was employed for the management of residual tumors following radiation therapy. Subsequently, it has been reported as the preferred treatment modality for UM [52]. This surgical procedure is categorized into two types: external resection, which involves the removal of the entire tumor through a scleral incision, and internal resection, which entails the removal of the entire tumor via the vitreous. External resection is typically indicated for melanomas of the iris, ciliary body, and peripheral choroid, whereas internal resection is indicated for choroidal melanomas situated posterior to the equator. The local excision of the tumor facilitates the acquisition of fresh tissue specimens for histopathological examination and genetic analysis, while also preserving ocular integrity and vision. In cases where tumor remnants are present on the scleral surface or the tumor is in proximity to the surgical margins, local excision may be augmented with adjunctive compressive radiation therapy to mitigate the risk of recurrence. Although the outcomes of local tumor excision are generally favorable, the procedure is technically demanding and necessitates a high level of surgical expertise and skill.

The established surgical criteria for the local excision of uveal melanoma (UM) include [53]: (1) a maximum tumor base diameter of $\leqslant$ 15 mm; (2) absence of local infiltration, with no involvement of the sclera or orbit; and (3) absence of systemic metastasis. Conversely, contraindications for surgical intervention include [53]: (1) extraocular infiltration or distant metastasis; (2) systemic conditions precluding surgical tolerance; and (3) the presence of flat, diffuse-shaped tumors, among others. The primary complications associated with the local excision of tumors encompass retinal detachment, proliferative vitreoretinopathy, and hemorrhage.

Eyeball removal

Enucleation is indicated for large and advanced uveal melanoma (UM), characterized by a tumor base diameter exceeding 20 mm or a thickness greater than 12 mm, as well as in cases involving optic nerve invasion, orbital extension, or secondary glaucoma [54].

Orbital content removal

In instances where UM extends into the orbit, an orbital exenteration procedure is performed, with efforts made to preserve the eyelids to promote expedited postoperative recovery.

Treatment for distant metastasis of UM

Currently, there is no definitive and effective treatment for distant metastasis of UM. For isolated metastatic lesions in the liver, local interventions such as perfusion, embolization, and ablation may be considered, alongside

other recommended approaches including immunotherapy, cytotoxic regimens, and targeted therapy [55]. For patients with confirmed distant metastases, participation in clinical trials is advised when feasible.

Recommendations for UM therapy

Treatment for UM is tailored to the individual. Radiation therapy is the most commonly employed method for managing UM, particularly for small to medium-sized tumors. In cases of large tumors, enucleation is the prevalent treatment option. For patients with specific indications, local excision of the tumor, TTT, and particle radiation therapy can also yield favorable therapeutic outcomes. UM is characterized by mutations in key oncogenes, abnormalities in signaling pathways, and epigenetic imbalances. Research targeting the pathogenesis of UM may offer new opportunities for the development of molecularly targeted therapies.

HISTOPATHOLOGICAL DIAGNOSIS

Histopathologic features

UMs exhibit considerable variability in their gross morphology, presenting as dome-shaped, mushroom-shaped, or flat and diffuse lesions. The tumors may be pigmented, non-pigmented, or a combination of both. Choroidal melanomas that breach Bruch's membrane and assume a mushroom shape are prone to extrusion through this membrane, leading to vasodilatation and congestion within the tumor vasculature. Extraocular dissemination of UM typically occurs via the vortex veins or through the nerves and blood vessels traversing the sclera. Choroidal melanomas predominantly exhibit vertical growth and may penetrate Bruch's membrane, extending into the eye, potentially crossing the retina into the vitreous body, or spreading through the scleral channels or directly infiltrating the sclera, thereby extruding and infiltrating in both inward and outward directions.

The histopathological classification of UMs is divided into four categories: spindle-cell, epithelioid cellular, mixed-cellular, and necrotic types. Melanomas composed of at least 90% spindle cells are classified as spindle cell melanomas, while those predominantly consisting of at least 90% epithelioid cells are designated as epithelioid cell melanomas. Tumors containing at least 10% epithelioid cells and up to 90% spindle cells are categorized as mixed-cell melanomas, which constitute the most common subtype. The primary immunohistochemical markers employed in the identification of UM include S-100 protein, anti-melanoma specific antibody (HMB-45), Melan-A, SRY-box transcription factor 10 (SOX10), and Vimentin [56, 57].

Histopathologically

Prognostic factors relevant to the prediction of UM outcomes include tumor cell type, mitotic activity, the mean diameter of the nucleoli of the 10 largest tumor cells, microvessel density, extravascular stroma pattern, and the number of tumor-infiltrating lymphocytes and macrophages [58] (Figure 3).

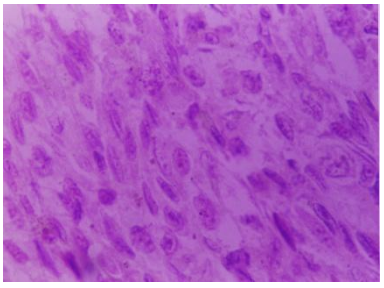

Figure 3: Histopathology of Choroidal Melanoma (HE×400). The tumor cells are spindle-shaped, with nuclear membrane folds forming striations in the center of the nucleus.

Table 4. Metastasis Risk Levels and Characteristics of Uveal Melanoma.

Risk Level	Detected Genes	Primary Tumor Characteristics (T) in TNM Staging	Tumor Histological Type	Follow-up Recommendations
Low Risk	Disomy of chromosome 3, gain of chromosome 6p, EIF1AX gene mutation	T1	Spindle cell type	Monitor every 12 months
Intermediate Risk	Disomy of chromosome 3, SF3B1 gene mutation	T2 and T3	Mixed cell type	Monitor every 6 to 12 months within 10 years
High Risk	Monosomy of chromosome 3, gain of chromosome 8q, BAP1 gene mutation, PRAME gene mutation	T4	Epithelioid cell type	Monitor every 3 to 6 months in the first 5 years, then every 6 to 12 months in the following 5 years

FOLLOW-UP AND PROGNOSIS

The management of UM necessitates regular monitoring of both ocular and systemic health. Post-radiation therapy, emphasis should be placed on evaluating the tumor and its associated complications, alongside the patient's overall health. In contrast, following enucleation, the primary focus should be on the patient's general condition.

A thorough ophthalmologic assessment is essential during follow-up visits, encompassing evaluations of visual acuity, intraocular pressure, and fundus condition, the latter being assessed after pupil dilation. Additionally, color photography and ultrasonography are indispensable for evaluating local tumor control. Techniques such as ultra-wide angle fundus imaging and fluorescein fundus angiography (FFA) are valuable for assessing peripheral fundus tumors and retinal vascular perfusion post-radiation therapy. Tumor recurrence predominantly occurs at the tumor margins, with central tumor recurrence and extraocular spread being less frequent.

Following the administration of radiation therapy, it is imperative to conduct follow-up examinations every 3 to 6 months during the initial two years, and subsequently every 6 to 12 months, to monitor for tumor recurrence and other potential complications. When available, genetic testing can be utilized to classify the metastatic risk grade, which, when integrated with the clinicopathological characteristics of the tumor, informs the postoperative follow-up strategy for patients (Table 4). The 5-year recurrence rate for small UM tumors following palliative radiation therapy is 6%, and the 10-year recurrence rate is 11%. In contrast, the 5-year recurrence rate for large UM tumors is 13%. It is crucial to differentiate between tumor recurrence and inadequate tumor regression, the latter indicating nonresponsiveness to treatment. Recurrence is associated with an elevated risk of metastasis development [55].

The tumor's volume and its proximity to the optic disc and macula are critical determinants of the patient's visual prognosis. The primary factors contributing to the effects of PBRT on patients' vision include radiation retinopathy, radiation optic neuropathy, and cataracts. Although the peak incidence of radiation retinopathy occurs within five years post-radiation therapy, approximately 7% of patients develop related lesions 7-10 years following treatment [59]. Furthermore, about 69% of patients experience vision loss within a decade post-surgery, necessitating long-term monitoring for radiation retinopathy. Concurrently, periocular or intravitreal administration of tretinoin or anti-vascular endothelial growth factor (anti-VEGF) agents, and/or panretinal photocoagulation, may be employed to manage the condition [60].

Patients diagnosed with UM require comprehensive monitoring to facilitate the early detection of metastatic lesions. This monitoring predominantly involves liver-specific imaging, abdominal ultrasonography, and enhanced MRI, as well as enhanced CT scans of the chest,

abdomen, and pelvis. Whole-body PET-CT may also be employed when necessary. Additionally, it is essential to provide thorough psychological evaluation, counseling, and support to assist patients in managing ocular or systemic discomfort, visual disturbances, alterations in appearance, and negative emotions such as worry, anxiety, and frustration regarding their future health, which may arise during treatment and follow-up.

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Member of the Expert Group on Formation Guidelines Penning experts

Yi Shao	Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine
Jian-Min Ma	Beijing Tongren Hospital, Capital Medical University
Hua-Sheng Yang	Zhongshan Ophthalmology Center, Sun Yat sen University
Yan Lou	China Medical University
Wen-Chang Wu	Wenzhou Medical University
Xiao-Ming Huang	Sichuan Eye Hospital
Xin-Ji Yang	General Hospital of the Chinese People's Liberation Army
Gang Tan	The First Affiliated Hospital of University of South China
Sheng-Li Hao	The Second Hospital of Tianjin Medical University
Li-Min Zhu	Tianjin Medical University Eye Hospital
Rui-Li Wei	The Second Affiliated Hospital of Naval Military Medical University
Chong-Gang Pei	The First Affiliated Hospital of Nanchang University
Tong Wu	Sichuan Eye Hospital
Hong-Gang Liu	Peking Tongren Hospital, Capital Medical University
Xiao-Wei Liu	Peking Union Medical College Hospital
Guang-Yu Li	The Second Hospital of Jilin University
Ai-Jun Deng	Affiliated Hospital of Shandong Second Medical University
Jing Li	Beijing Tongren Hospital, Capital Medical University
Jia Tan	Xiangya Hospital, Central South University
Kai-Jun Li	Shenzhen Ophthalmic Hospital Shenzhen Institute of Ophthalmic Disease Control and Prevention
Wei Wu	Chinese PLA General Hospital
Shi-Yin Li	Xiamen University Xiang'an Hospital
Wei Chi	Shenzhen Ophthalmic Hospital Shenzhen Institute of Ophthalmic Disease Control and Prevention
Xuan Liao	Affiliated Hospital of North Sichuan Medical College
Gang-Jin Kang	The Affiliated Hospital of Southwest Medical University
Ming-Zhi Zhang	Shantou International Eye Center, Shantou University-Chinese University of Hong Kong
Wei-Hua Yang	Shenzhen Ophthalmic Hospital Shenzhen Institute of Ophthalmic Disease Control and Prevention
Liang Hu	The Affiliated Eye and Vision Hospital of Wenzhou Medical University
Wen-Si Tao	Bascom Palmer Eye Hospital,

	USA
Wen-Li Yang	Peking Tongren Hospital, Capital Medical University
Yao-Hua Wang	Eye Hospital of Nanchang University
Hui Zhang	The First Affiliated Hospital of Kunming Medical University
Jian-Qi Cai	China National Institute of Standardization
Li Zhou	The First Affiliated Hospital of Nanchang University
Dan Ji	Xiangya Hospital, Central South University
He Dong	Dalian No.3 People's Hospital
Yang Liu	Zhongnan Hospital of Wuhan University
Jian Ma	The Second Affiliated Hospital of Zhejiang University School of Medicine
Li Zhou	The First Affiliated Hospital of Nanchang University Hospital
Ying Jie	Beijing Tongren Hospital, Capital Medical University
Wen-Qing Shi	Jinshan Hospital, Fudan University
Juan Peng	The Second Affiliated Hospital of Guangzhou Medical University
Feng Wang	Meizhou People's Hospital
Zhong-Wen Li	Ningbo Eye Hospital, Wenzhou Medical University
Guang-Hui Liu	People's Hospital of Fujian University of Traditional Chinese Medicine
Wen-Jin Zou	The First Affiliated Hospital of Guangxi Medical University
Zhi-Hong Deng	The Third Affiliated Hospital of Central South University
Cheng Li	Xiamen University Eye Institute
Yi Liu	Nanjing Hospital of Traditional Chinese Medicine Affiliated with Nanjing University of Chinese Medicine
Bi-Lian Ke	Shanghai Renji Hospital, Shanghai Jiao Tong University School of Medicine
Lei Shi	Anhui Eye Hospital, the Second Affiliated Hospital of Anhui Province
Xin Wen Sun	Yat-Sen Memorial Hospital, Sun Yat-Sen University
Rui-Bo Yang	Tianjin Medical University Eye Hospital
Lei Tian	Beijing Tongren Hospital, Capital Medical University
Yao Yu	The First Affiliated Hospital of Nanchang University
Yi-Ping Jiang	The First Affiliated Hospital of Gannan Medical University
Xiang-Long Yi	First Affiliated Hospital of Xinjiang Medical University
Dan Wen	Xiangya Hospital, Central South University
Xia Hua	Tianjin Aier Eye Hospital
Kai Wu	The First Affiliated Hospital of Nanhua University
Sha Wang	Xiangya Hospital, Central South University
Xiu-Sheng Song	Enshi Tujia and Miao Autonomous Prefecture Central Hospital
Hua-Tiao Xie	Union Hospital, Tongji Medical College, Huazhong University of Science and Technology
Qing Zhang	The Second Affiliated Hospital of Anhui Medical University
Ying-Li Li	Zhujiang Hospital, Southern Medical University
Qian-Min Ge	The First Affiliated Hospital of Nanchang University
Cheng-Wei Lu	First Baiqiuen Hospital of Jilin University
Qi-Chen Yang	West China Hospital of Sichuan University
Qi Li	The First Affiliated Hospital of Chongqing Medical University
Chun-Hua Liu	West China Hospital, Sichuan University
Yan Ji	The First Affiliated Hospital of Chongqing Medical University
Yong-Yi Niu	Guangdong Provincial People's Hospital

Xue-Zhi Zhou	Xiangya Hospital, Central South University
Yan-Lei Chen	Guangdong Provincial People's Hospital
Bin Li	Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine
Li-Juan Luo	Xiaoshan Hospital, Affiliated with Hangzhou Normal University
Jun Liu	The 924th Hospital of the Joint Logistics Support Force of the Chinese People's Liberation Army
Xian-Mei Zhou	North Sichuan Medical College

Experts involved in the drafting (in alphabetical order of surnames)

Jing-Hua Bu	Xiamen University Xiang'an Hospital
Cheng Chen	The First Affiliated Hospital of Nanchang University
Bo Chen	Sichuan Provincial People's Hospital
Jing-Yao Chen	Yan'an Hospital, Kunming Medical University
Jun Chen	Jiangxi University of Traditional Chinese Medicine
Xin-Jian Chen	Suzhou University
Xu Chen	Maastricht University, the Netherlands
Yu Chen	Shanghai University
Che Cheng	Changsha Aier Eye Hospital
De-Yong Deng	Yueyang Hospital of Integrative Medicine, Shanghai University of Traditional Chinese Medicine
Yu-Qing Deng	Zhongshan Eye Center, Sun Yat-sen University
Zhi-Xin Geng	Tianjin Sida Jia Technology Co
Yi Han	Xiamen University Eye Institute
Liang-Qi He	The First Affiliated Hospital of Nanchang University
Yuan He	The Second Affiliated Hospital of Xi'an Medical College
Jin-Yu Hu	First Affiliated Hospital of Nanchang University
Shou-Long Hu	Henan Provincial Children's Hospital
Cai-Hong Huang	Xiamen University Eye Institute
Li-Juan Huang	The Second Affiliated Hospital of Fujian Medical University
Ming-Hai Huang	Nanning Aier Eye Hospital
Yong-Zhi Huang	West China Hospital of Sichuan University
Hong-Hua Kang	Xiamen University Eye Institute
Min Kang	The First Affiliated Hospital of Nanchang University
Hsuanyi Lee	Columbia University Mailman School of Public Health
Ke-Ran Li	The Affiliated Eye Hospital of Nanjing Medical University
Ying-Jie Li	The Third Affiliated Hospital of Nanchang University
Juan Li	Shanxi Eye Hospital
Nai-Yang Li	Zhongshan People's Hospital
Qing-Jian Li	Huashan Hospital, Fudan University
San-Ming Li	Harvard Medical School
Zhi-Yuan Li	Chenzhou First People's Hospital
Rong-Bin Liang	Jinshan Hospital, Fudan University
Xu-Lin Liao	Hong Kong Eye Hospital
Jing-Wei Lin	Xiamen University Eye Institute
Xiang Lin	Xiamen University Eye Institute
Zhi-Rong Lin	Xiamen Eye Center, Xiamen University
Qian Ling	The First Affiliated Hospital of Nanchang University
Qiu-Ping Liu	The First Affiliated Hospital of Nanhua University
Sheng-Tao Liu	Eye, Ear, Nose and Throat Hospital of Fudan University

Ting-Ting Liu	Shandong Eye Hospital
Xiang-Yi Liu	The First Affiliated Hospital of Nanchang University
Yuan Liu	Miller School of Medicine
Ze-Yu Liu	Xiamen University Eye Institute
Zhao-Lin Liu	The First Affiliated Hospital of Nanhua University
Zuo-Zhou Liu	Xiamen University Eye Institute
Shang-Kun Ou	Affiliated Hospital of Guizhou Medical University
Jun Ouyang	Jiujiang First People's Hospital
Wei Qiang	Ningbo Eye Hospital, Wenzhou Medical University
Kun-Liang Qiu	Shantou International Eye Center, Shantou University-Chinese University of Hong Kong
Ting-Ting Shao	Eye, Ear, Nose and Throat Hospital of Fudan University
Ting Su	Renmin Hospital of Wuhan University
Li-Ying Tang	Zhongshan Hospital, Xiamen University
Wen-Si Tao	Bascom Palmer Eye Institute
Li-Yang Tong	Ningbo Eye Hospital, Wenzhou Medical University
Hai-Yan Wang	Shaanxi Eye Hospital
He Wang	Affiliated Hospital of Xuzhou Medical University
Sun Wang	The First Affiliated Hospital of Xinxiang Medical College
Xiao-Yu Wang	The First Affiliated Hospital of Nanchang University
Xue-Lin Wang	The First Affiliated Hospital of Jiangxi Medical College
Yan Wang	The Affiliated Hospital of Inner Mongolia Medical University
Yi-Xin Wang	Cardiff University, UK
Hong Wei	The First Affiliated Hospital of Nanchang University
Qian Wei	Imperial College London
Yan-Tao Wei	Zhongshan Ophthalmic Center, Sun Yat-sen University
Jie-Li Wu	Changsha Aier Eye Hospital
Yang Wu	Xiamen Hospital, Zhongshan Hospital, Fudan University
Zhen-Kai Wu	Changde First People's Hospital
Wei Xia	The First Affiliated Hospital of Suzhou University
San-Hua Xu	The First Affiliated Hospital of Nanchang University
Yong Yao	Guangzhou Sigma Lin Shunchao Eye Hospital
Hai-Jun Yang	Nanchang Purui Eye Hospital
Qing-Hua Yang	General Hospital of the Chinese People's Liberation Army
Shu Yang	Kunming First Hospital
Yi-Ran Yang	Henan Provincial Eye Hospital
Yu-Li Yang	First Affiliated Hospital of Army Military Medical University
Yi-Feng Yu	The Second Affiliated Hospital of Nanchang University
Qing Yuan	Jiujiang First People's Hospital
Yan-Mei Zeng	The First Affiliated Hospital of Nanchang University
Bing Zhang	Hangzhou Children's Hospital
Yu-Qing Zhang	The Second Affiliated Hospital of Chongqing Medical University
Zhen Zhang	The First Affiliated Hospital of Xiamen University
Yan-Yan Zhang	Ningbo Eye Hospital, Wenzhou Medical University
Hui Zhao	The First People's Hospital of Shanghai Jiaotong University School of Medicine
Qin-Xiang Zheng	The Affiliated Optometry Hospital of Wenzhou Medical University
Jing Zhong	Zhongshan Ophthalmic Center, Sun Yat-sen University
Sheng Zhou	Institute of Biomedical Engineering, Chinese Academy of Medical Sciences
Pei-Wen Zhu	Eye, Ear, Nose and Throat Hospital, Fudan University
Xin-Yue Zhu	The First People's Hospital of Shanghai Jiao Tong University School of Medicine
Zhuo-Ting Zhu	University of Melbourne Eye Center
Jie Zou	The First Affiliated Hospital of Nanchang University

Guidance Statement

All the experts involved in the development of this guideline declare that they adhere to an objective position, based on professional knowledge, research data and clinical experience, and that this guideline is formed after full discussion and unanimous agreement of all the experts.

Disclaimer

The contents of this guideline represent only the guidance of the experts involved in the development of this guideline for the reference of clinicians. Despite extensive consultation and discussion among experts, there are incomplete points. The recommendations provided in this guideline are not mandatory, and practices that are inconsistent with this guideline do not imply error or inappropriateness. There are still many issues to be explored in clinical practice, and ongoing and future clinical trials will provide further evidence. With the accumulation of clinical experience and the emergence of new treatments, this guideline will need to be revised and updated periodically in the future to bring more clinical benefits to the subjects.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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