Chapter

Basis, Diagnosis, and Treatment of Uveal Melanoma

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Abstract

Uveal melanoma (UM) is the most common primary intraocular malignancy with a strong tendency to metastasize. The prognosis is poor once metastasis occurs. The treatment remains challenging for metastatic UM, even though our understanding of UM has advanced. Risk factors for developing UM include ages, skin colors, and genetic mutations. Many therapies that have applied to cutaneous melanoma have little or no success in UM. Various forms and combinations of radiotherapy, phototherapy, and local resection are utilized for advanced cases. The treatment aims to preserve the eye and useful vision and prevent metastases. This chapter aims to introduce the current study for UM.

Keywords: ophthalmology, uveal melanoma, pathogenesis, diagnosis, pathological features, staging, treatment, prognosis

1. Introduction

Uveal melanoma (UM) is the most common primary malignant intraocular tumor in adults. As a highly aggressive and fatal tumor, it mostly occurs in the choroid (90.0%), followed by the ciliary body (6.0%) and the iris (4.0%). The mean patient age at diagnosis was between the ages of 50 and 60, mostly in Europeans, Americans, and Caucasians, and more men than women. Despite effective treatment of the primary tumor and metastases, 50% of patients develop liver metastases within a median of 2.4 years [1]. Once UM metastasizes throughout the body, there is no effective treatment. Overall, 90% of patients die within 6 months of diagnosis of metastases [2, 3]. However, metastases are detectable in only 1–3% of diagnosed cases. Because the survival rate of patients is closely related to the size of the primary tumor, early diagnosis and early local treatment are crucial. At present, the main treatment methods include enucleation and applicator radiotherapy, but no standard treatment plan has been established for postoperative adjuvant therapy and systemic treatment for advanced patients.

2. Pathogenesis of UM

The occurrence and development of UM involve multi-factors, multi-stages, and multi-gene variation accumulation.

1. **Cytogenetics:** One of the risk factors for UM metastasis is chromosomal variation, including gain of chromosome 1q, 6p, 8q and deletion of chromosome 1p, 3, 6q, 8p, 9p [4]. Chromosome 3 deletion exists in more than 50% of primary UM and is a high-risk prognostic factor for tumor metastasis [5]. Meanwhile, chromosome 3 deletion can also be accompanied with other chromosomal abnormalities. Studies have shown that when chromosome 3 and 1p are deleted, the survival time of UM patients is significantly shortened [6], and if chromosome 3 deletion and chromosome 8q gain are found in tumors, the prognosis is poor [7]. The combination of chromosome 3 deletion and chromosome 6p gain in UM patients has a better prognosis than the presence of chromosome 3 alone [8].

2. **Gene expression profile:** A number of research results have confirmed that gene expression profiles can provide people with more accurate prognostic assessment than cytogenetic, pathological features, and clinical information [9]. Onken et al. [10] detected the expression of 12 differential genes and 3 control genes in UM, and found the gene expression profile of UM. According to these genes, they divided UM into 2 types: type 1 has a lower risk of metastatic spread, while type 2 has a higher risk of metastatic spread. Their founding provided an accurate, practical, and convenient method for predicting the prognosis of UM metastasis. In more than 100 clinical research centers in the United States and Canada, the 15-gene detection chip (trade name: Decision Dx-UM) has been used as a routine examination to screen high-risk groups for early metastasis of UM [11].

3. **Gene mutation:** Currently, the most studied mutated genes in UM are GNAQ, GNA11, and BAP1. Other mutated genes include EIF1AX and SF3B1. While EIF1AX and SF3B1 are associated with good and better prognosis in UM, respectively, BAP1 mutations predict poor prognosis and risk of tumor spread [12–15]. Van Raamsdonk CD et al. found that the mutation frequency of oncogene GNAQ in UM was 40%, and the mutation frequency of GNA11 was 45% [16, 17]. The mutation frequency of GNAQ gene in Chinese UM was as high as 51.9%, and the mutation rate of GNAll gene was 25.9% [18]. Chen et al. [19] found that mutations in GNAQ or GNA11 genes lead to the development of UM through the activation of their downstream signaling pathways PKC and MAPK. Yu et al. [20] and Feng et al. [21] found that GNAQ or GNAll gene mutations lead to excessive activation of YAP protein, resulting in uncontrolled tumor cell proliferation and malignant tumors.

BAP1 (BRCA1-Associated Protein 1) is an important tumor suppressor gene. Wiesner et al. [22] found that the patients suffering from uveal and skin melanoma are related to the abnormal expression of the BAP1 family. BAP1 can regulate the cell cycle, cell differentiation, apoptosis, DNA damage response, and gene expression [23]. Due to the key regulatory role of BAP1 on cells, the decreased gene expression or gene mutation is related to the occurrence and development of various malignant tumors, but its specific mechanism has not yet been elucidated [24]. The loss of BAP1 is associated with the loss of chromosome 3 in UM cells, and the loss of chromosome 3 in UM cells is a risky prognostic factor for the occurrence of metastasis in

UM [25–29]. SF3B1 mutation exists in 19% of UM, which suggests that UM has a better prognosis [30]. Mutations in SF3B1 cause a large amount of mRNA alternative splicing, but how it promotes UM remains unclear. Martin et al. [31] found that 24% of UM had mutations in EIFIAX, which had a good prognosis. The protein encoded by EIF1AX is involved in protein translation, but the specific mechanism between its mutation and the development of UM is still unclear.

4. **Non-coding RNA:** Both miRNA and long non-coding RNA (lncRNA) belong to non-coding RNA, and both play a regulatory role in the occurrence and development of UM.

miRNAs are a group of endogenous RNAs that can directly bind to mRNA and regulate gene expression after transcription. miRNAs are involved in the development process of almost all malignant tumors, including cell proliferation, differentiation, apoptosis, and metastasis mechanisms. In recent years, miRNA has attracted much attention in the field of tumor research. Scientists have analyzed the miRNA expression profile of UM, and a variety of miRNAs have been found to be associated with the prognosis of UM. The genes encoding these miRNAs are considered novel oncogenes and tumor suppressors. For example, both miRNA-130a and miRNA26a exhibit tumor suppressor properties when overexpressed [32, 33].

lncRNAs play a crucial role in the maintenance of cellular homeostasis and participate in many key cellular pathways. In cancer, lncRNAs are associated with apoptosis evasion, proliferation, invasion, and drug resistance. Among them, autophagy-related lncRNA plays an important role in predicting the prognosis of UM patients. The lncRNA RHPN1-AS1 is oncogenic and can suppress UM cell proliferation by silencing its expression [34].

3. Diagnosis

3.1 Symptoms and signs

UM includes melanoma that occurs in the iris, ciliary body, and choroid, and can spread outside the eye, with various clinical symptoms and many complications. Various symptoms and signs appear depending on the site of occurrence. UM can be divided into four stages according to clinical manifestations: intraocular stage, glaucoma stage, extraocular extension stage, and systemic metastasis stage.

The clinical symptoms of choroidal melanoma are diverse, and the ocular symptoms are the most prominent. Symptoms such as vision loss, visual obstruction, metamorphopsia, or discoloration often appear, and the symptoms vary with the location of the tumor. If the tumor is located in the macular area, the early subjective symptoms are metamorphopsia, microopia or macroopia, changes in color vision. Visual field defects may have relative or absolute scotoma, or persistent hypermetropia, or floating in front of the eyes. When the tumor is located in the peripheral part of the fundus, there may be no symptoms. The morphology of choroidal melanoma is divided into three types, namely dome-shaped, mushroom-shaped, and flat diffuse. The melanoma in the choroid often causes exudative retinal detachment, sometimes with vitreous hemorrhage, causing blurred vision.

In iris melanoma, raised lesions in dark brown with clear edges can be seen on the surface of the iris, and dilated "sentinel vessels" can be seen on the surface of the sclera. The OCT examination of the anterior segment showed that there was a circular raised lesion on the surface of the iris, and the anterior surface of the tumor was echogenic; the internal echo of the tumor was attenuated, and imaging could not be performed on the posterior surface.

The location of the ciliary body is hidden and difficult to observe. It is difficult to detect tumors in its location early, because ciliary body melanoma may not have any specific clinical manifestations in the early stage. Ciliary body melanoma can grow forward, backward, and toward the vitreous cavity and sclera, and the clinical manifestations of ciliary body tumors can be different depending on the extent of ciliary body tumor invasion. Ciliary body melanoma can lead to clinical manifestations such as glaucoma, uveitis, lens displacement to varying degrees, diopter changes, vitreous hemorrhage, retinal detachment, and macular edema.

Intraorbital spread of UM: (1) spread along the scleral duct and scleral vortex vein; (2) directly invade the sclera and spread to the outside of the eyeball; (3) directly spread along the cribriform plate; (4) invade the retina, ciliary body, and iris, conjunctiva. The way of extraocular extension of UM is related to the growth location of the tumor. Extraocular extension occurred in the front of the equator, and black nodules can be seen in the conjunctiva, which can be misdiagnosed as scleral staphyloma. The posterior part of the globe spreads, with exophthalmos, eyelid edema, and ocular motility disturbances. Although no tumor was palpable on the orbital rim, the orbital pressure was high and the eyeball could not move back. In severe cases, the eyeball protrudes outside the palpebral fissure, and the surface structure of the eyeball is damaged and uneven. Due to massive necrosis of tumor tissue, panophthalmitis, hypopyon, and orbital cellulitis may occur.

3.2 Eye examination

A comprehensive examination should be performed including vision, intraocular pressure, anterior segment, and fundus. Slit-lamp microscopy and indirect ophthalmoscopy are the main examination methods in ophthalmology, and sometimes gonioscopy or transillumination examination is also required. All patients underwent evaluation of the anterior segment using slit-lamp microscopy and the posterior segment using indirect ophthalmoscopy to determine tumor location, shape, pigmentation, vascularity, tumor margin morphology, distance from the macula, optic disc, and ciliary body and corneal involvement, anterior scleral extension. The evaluation is required to determine whether there are secondary lesions such as malignant transformation of choroidal nevi, such as sentinel vessels on the surface of the sclera, cataracts, subretinal fluid, or orange pigment in the tumor. Gonioscopy can identify involvement of the anterior chamber angle by iris or ciliary body melanoma. Transillumination is performed by transscleral or pupillary illumination to determine the degree of ciliary body involvement.

3.3 Auxiliary inspection

In recent years, with the development of imaging technology, especially the application of ocular ultrasound, CT, MRI, and fundus angiography, the diagnostic accuracy of UM has been greatly improved.

1. Compared with other imaging examinations, B-ultrasound and color Doppler blood flow imaging ultrasonography have unique advantages such as fast, accurate, economical, non-invasive, and repeatable operations. When applying B-ultrasound examination, the main features of UM are as follows: (a) The tumor grows in a fungating or dome-like shape; (b) on the sonogram, the echo is dense and strong at the front edge of the mass, and the echo intensity gradually decreases backward. An echo-free area is formed close to the bulb wall, which is the so-called "hollow out phenomenon;" (c) choroidal indentation sign; and (d) melanin cells in the tumor body carcinogenic sound wave reversal reaction are blocked and the image of the corresponding orbital area is covered. Color Doppler flow imaging (CDFI) can directly display the blood supply of the lesion and clarify the source of the blood supply, which is of great significance for the differential diagnosis of benign and malignant lesions. UM is a solid tumor composed of pigmented cells such as spindle cells and epithelioid cells. The blood supply in the tumor comes from the posterior ciliary vasculature of the branch of the ophthalmic artery. CDFI detection shows that the rich blood flow signals in the UM can be distributed in the whole tumor body in the form of "branches," showing a pure arterial blood flow spectrum, which is the same as the blood flow characteristics of the posterior ciliary artery. The emergence of CDFI technology makes up for the lack of blood flow imaging in ordinary ultrasound diagnosis and provides a new diagnostic method for eye diseases, especially diseases related to blood flow.

2. CT and MRI: UM in the early CT plain scan only shows localized thickening of the eye ring; when the tumor protrudes into the vitreous cavity, it appears as an iso-density or slightly high-density hemispherical or spherical shape with uniform density and clear boundaries. Tumors in enhanced CT scans often show different degrees of enhancement. MRI is radiation-free, multi-parameter, and multi-directional imaging, with high resolution of soft tissue, no bone artifact interference, and dynamic enhancement, which has great advantages in the examination of eye lesions. The main MRI manifestations of UM are as the following: Compared with the cerebral cortex signal, the tumor body mostly shows high signal on T1WI and low signal on T2WI, that is, short T1 signal and short T2 signal. Most of the UM showed mild enhancement after enhanced scanning. The UM-specific signal change is mainly due to the fact that melanin contained in the tumor is a paramagnetic substance that shortens the relaxation time of T1 and T2. Therefore, CT and MRI have important application value in the diagnosis of UM.

3. Fluorescein fundus angiography (FFA) and indocyanine green angiography (ICGA): A large number of melanin granules in UM tumors cause fluorescence shielding. In the early phase of FFA examination, the local manifestations are weak fluorescence, and the fluorescent spots in the tumor body gradually increase in the arterial-venous phase, forming mottled fluorescence with alternating intensity and weak fluorescence in the low fluorescence area. Tumors can be seen tortuous, spiral-shaped tumor blood vessels and retinal blood vessels can be imaged at the same time as a double loop phenomenon, and in the late phase, the imaging shows diffuse fluorescence. ICGA plays an important role in the diagnosis of UM. In the ICGA examination tumors always have no fluorescence, or no fluorescence in the early phase, and weak fluorescence or spot-like fluorescence

or fusion fluorescence in the late phase. In some patients, large blood vessels can be seen during angiography, and in the late phase, fluorescence leakage occurs in tumors. Advanced tumors have emptying phenomenon or three-ring images in some patients. ICGA and FFA are the effective diagnostic and differential means for diagnosing UM. FFA can show the double circulation of the tumor and retinal telangiectasia, and ICGA is used as a supplementary inspection method of FFA. Both of them have important clinical value.

4. Optical coherence tomography (OCT): OCT can show subtle retinal abnormalities, such as subretinal fluid, intraretinal edema, irregular photoreceptor layer, choroidal capillaries compressed by tumors, and orange pigment and cross-sectional architecture of choroidal lesions. Compared with ultrasonography, OCT is more advantageous in measuring small choroidal melanoma (thickness < 3 mm) [35]. OCT of the anterior segment is suitable for the detection of iris melanoma, but the basal margin of the tumor may be blurred by hyperpigmentation. The OCT angiography in Fundus can also be used to monitor macular microangiopathy after radiotherapy providing evidence for clinical treatment [36].

5. Positron emission computed tomography (PET) CT: PET-CT scanning has high sensitivity and predictive value for monitoring systemic metastasis in UM patients. For patients with suspected UM metastasis, PET-CT examination should be performed. It can detect metastasis early and stage the tumor, which is of great value for the treatment and follow-up of patients. In addition, PET-CT can also be used to find the primary tumor of choroidal metastases [37].

4. Pathological features

UM originates from uveal melanocytes, which is limited in the early stage, and further develops into typical fungal changes. Under the electron microscope, UM tumors are composed of round and spindle cells with rich cytoplasm, large nuclei, and frequent mitotic phases. New blood vessels are scattered in the tumor. Most tumors contain melanin, and a few tumors do not. The histopathological classification of UM is currently widely adopted in the world according to the classification standard developed by the WHO in 1980, and it is divided into four categories: (a) spindle cell type: composed of spindle-shaped type A and type B tumor cells in different proportions. Tumor cells are relatively dense, arranged in bundles or swirls. (b) Epithelial cell type: The tumor body is mainly composed of epithelioid tumor cells. Epithelioid cells account for more than 75%, and the rest are spindle-shaped A cells or spindle-shaped B cells. (c) Mixed cell type: composed of spindle-shaped and epithelioid melanoma cells in different proportions. (d) Others: those that do not meet the above classification, such as necrotic type, balloon-like cell type.

Spindle cell melanoma accounts for 40% of all UM, of which more than 90% are spindle cells, and the 15-year mortality rate of patients is 20%; epithelial cell melanoma accounts for 3–5% of all UM, of which more than 90% are epithelial cells, and the 15-year mortality rate of patients is 75%; the remaining 50% are mixed cell melanoma. At present, it is believed that epithelioid cell type UM is the most malignant and has the greatest risk of metastasis, followed by mixed type UM, and spindle cell type UM is the least malignant. The main immunohistochemical markers of UM include S-100, Melan-A, and Vimentin, etc.

5. Differential diagnosis

1. Scleral ciliary nevus: Scleral ciliary nevus is also called benign melanoma. It often occurs in the optic nerve area, followed by the uvea and conjunctiva. In terms of histology, this tumor is similar to benign tumors of the choroid, and its biological behavior is similar to that of pigmented nevus, and very few of them can become malignant. It can be distinguished by FFA, CT, and magnetic resonance examination. Despite this, if the intraoperative conditions permit, the scope of surgery should be determined after local excision of the tumor and frozen examination.

2. Iris implantation cyst: Malignant melanoma of the iris is clinically manifested by rich blood vessels in the tumor, a large amount of pigment loss, hemorrhage in the anterior chamber, pigment granules behind the cornea, inflammatory reaction on the surface of the iris, atrophy, and discoloration of the iris near the tumor. Traumatic implantation of iris cysts is the most common, mostly caused by penetrating eyeball injuries or intraocular surgery.

6. Staging

There are two main staging systems for UM, both based on tumor thickness and maximal basal diameter. The first staging system was formulated by the Collaborative Ocular Melanoma Study Group (COMS) [37], and the second was the TNM staging system proposed by the American Joint Committee on Cancer (AJCC) in 1968 [38]. In COMS staging, tumors are classified according to their thickness and largest basal diameter as small (1.5–2.4 mm thickness with the largest basal diameter 5–16 mm), medium (2.5–10.0 mm thickness with the largest base ≤16 mm in diameter), and large (thickness > 10.0 mm or maximal basal diameter > 16 mm). In TNM staging, tumors are classified into T1, T2, T3, and T4 stages, where "T" indicates the characteristics of the primary tumor, including tumor volume and its infiltrating relationship with surrounding tissues; "N" indicates the degree and scope of regional lymph node involvement; and "M" indicates distant metastasis of the tumor. There is partial overlap between small and medium tumors in the COMS staging and T1 and T2 in the TNM staging, and between large tumors in the COMS staging and T3 and T4 in the TNM staging. In the 8th edition of the TNM staging system launched by AJCC in 2018, more detailed staging was carried out for iris melanoma and the extrascleral extension of the tumor. The primary tumor is divided into T1-T4 stages according to clinical features, T1 stage is tumor limited to iris; T2 stage is tumor invaded ciliary body and (or) choroid; T3 stage is tumor invaded ciliary body and (or) choroid, with scleral infiltration; T4 stage is tumor with extrascleral extension. For ciliary body and choroidal melanoma staging, the eighth edition of the TNM staging system was also updated (**Table 1**).

UM is divided into N0 stage without lymph node involvement and N1 stage with lymph node involvement; M0 stage without metastasis; and M1 stage with metastasis, and is divided into M1a ~ M1c stage according to the size of metastatic lesions.

AJCC assessed the prognosis of patients according to TNM staging, and divided patients into 7 categories according to the assessed prognosis (**Table 2**) [39, 40].

T1 tumors: T1a: The T1-size tumor is not growing into the ciliary body or growing outside the eyeball. T1b: The T1-size tumor is growing into the ciliary body. T1c: The T1-size tumor is not growing into the ciliary body but is growing outside of the eyeball. The part of the tumor that is outside the eyeball is 5 mm (about 1/5 of an inch) or less across. T1d: The T1-size tumor is growing into the ciliary body and also outside of the eyeball. The part of the tumor that is outside the eyeball is 5 mm (about 1/5 of an inch) or less across.
T2 tumors: T2a: The T2-size tumor is not growing into the ciliary body or growing outside the eyeball. T2b: The T2-size tumor is growing into the ciliary body. T2c: The T2-size tumor is not growing into the ciliary body but is growing outside the eyeball. The part of the tumor that is outside the eyeball is 5 mm (about 1/5 of an inch) or less across. T2d: The T2-size tumor is growing into the ciliary body and also outside the eyeball. The part of the tumor that is outside the eyeball is 5 mm (about 1/5 of an inch) or less across.
T3 tumors: T3a: The T3-size tumor is not growing into the ciliary body and is not growing outside the eyeball. T3b: The T3-size tumor is growing into the ciliary body. T3c: The T3-size tumor is not growing into the ciliary body but is growing outside the eyeball. The part of the tumor that is outside the eyeball is 5 mm (about 1/5 of an inch) or less across. T3d: The T3-size tumor is growing into the ciliary body and also outside the eyeball. The part of the tumor that is outside the eyeball is 5 mm (about 1/5 of an inch) or less across.
T4 tumors: T4a: The T4-size tumor is not growing into the ciliary body or growing outside the eyeball. T4b: The T4-size tumor is growing into the ciliary body. T4c: The T4-size tumor is not growing into the ciliary body but is growing outside the eyeball. The part of the tumor that is outside the eyeball is 5 mm (about 1/5 of an inch) or less across. T4d: The T4-size tumor is growing into the ciliary body and also outside the eyeball. The part of the tumor that is outside the eyeball is 5 mm (about 1/5 of an inch) or less across. T4e: The tumor can be any size. It is growing outside the eyeball and the part of the tumor that is outside the eyeball is greater than 5 mm across.

Table 1.
AJCC TNM staging system (T categories for ciliary body and choroidal melanoma [39]).

Stage I	T1a, N0, M0
Stage IIA	T1b to T1d, N0, M0 OR T2a, N0, M0
Stage IIB	T2b or T3a, N0, M0
Stage IIIA	T2c or T2d, N0, M0 OR T3b or T3c, N0, M0 OR T4a, N0, M0
Stage IIIB	T3d, N0, M0 OR T4b or T4c, N0, M0
Stage IIIC	T4d or T4e, N0, M0
Stage IV	Any T, N1, M0 OR Any T, any N, M1

Table 2.
AJCC stage grouping.

7. Treatment

The individualized and comprehensive treatment should be applied to UM patients. The appropriate methods or a combination of multiple methods should be selected according to tumor size, location, shape, growth rate, visual acuity of the affected eye and fellow eye, and general conditions. Given that UM is not sensitive

to traditional radiochemotherapy (referred to as radiochemotherapy), enucleation was the only and effective treatment, but this operation has caused great damage to the patient's physiology and psychology, seriously affecting the quality of life. With the advancement of science and technology, new types of radiotherapy such as patch radiotherapy and particle radiotherapy can not only effectively kill tumors and preserve eyeballs, but also preserve part of effective vision. Compared with traditional radiotherapy, the local control rate is higher and complications are fewer. Therefore, eye protection therapy represented by patch radiotherapy and particle radiotherapy has become the first-line treatment for UM. Other treatments include transpupillary thermotherapy (TTT), photodynamic therapy (PDT), local resection of ocular tumors, enucleation, orbital content extraction, and immunotherapy.

7.1 Adhesive radiation therapy

Brachytherapy is a type of radiotherapy in which the radiation source is located next to the treatment target. It is the preferred treatment method for small and medium tumors in UM (the maximal diameter of the tumor base is ≤18 mm and the thickness is ≤10 mm). The goal is to deliver a higher localized radiation dose to the tumor with less damage to surrounding tissue. Currently, the radioactive isotopes commonly used in ophthalmology are 106 ruthenium, 125 iodine, 103 palladium, and 131 cesium [41, 42]. Brachytherapy can continue to give a lower radiation dose, and its radiation dose attenuates with distance (radiation dose = 1/(radiation distance)^2), so the dose distribution is roughly decreasing from the base of the tumor (adjacent to the applicator) to the apex of the tumor [43]. After radiation exposure, tumor cell DNA breaks, cell membrane permeability increases, cell division cycle arrests, cell proliferation decreases, and necrosis and apoptosis occur [44]. The 5-year and 12-year survival rates of the plaster treatment group for medium-volume (thickness 2.5–10 mm and maximal tumor base diameter < 16 mm) tumors reported by the famous Collaborative Ocular Melanoma Study Group (COMS) were 82% and 57% [45], which were no different from those in the enucleation group; at the same time, the 5-year cumulative local recurrence rate and enucleation rate were only 10.3% and 12.5% [46], and 1/3 of the patients could still retain better vision [47]. The main complications of patch radiotherapy are cataract, retinal detachment, glaucoma, radiation retinopathy, radiation optic neuropathy, etc.

7.2 Particle radiation therapy

Unlike previous photon radiotherapy (including X-rays, alpha, beta, and gamma rays released by isotopes, etc.), particle radiotherapy is a radiation therapy that uses charged particles as radiation sources, including protons, carbon ions, helium ions, etc. Particle radiotherapy has the characteristics of the Bragg peak; that is, after the particle beam obtains energy through the accelerator, it is injected into the human body under precise control and the energy is concentratedly released to the lesion, killing the lesion cells, and at the same time, the energy decays sharply and falls back, forming the Bragg peak [48]. Therefore, particle radiation therapy has little damage to surrounding normal tissues. Due to its good targeting, and uniform dose distribution, it becomes the first choice for UM radiation therapy. It is reported that the eye protection rate of proton radiotherapy is above 85%, the 5-year survival rate is above 80% [49–51], and the 5-year local control rate and disease-related survival rate after heavy ion therapy are 92.8% and 82.2% [52]. It is more suitable for the treatment of difficult

tumors near the macula or optic disc [53, 54]. Compared with patch radiotherapy, particle radiotherapy represented by protons and heavy ions has a higher local tumor suppression rate and a lower tumor recurrence rate, which provides an important reference for clinicians to choose treatment in the future. Common complications of particle radiotherapy include cataract, retinal detachment, ocular surface changes, glaucoma, macular degeneration, and radiation-induced fundus lesions.

7.3 Transpupillary thermotherapy (TTT)

TTT is a non-invasive treatment. The 810 nm infrared diode laser is delivered to the inside of the choroidal tumor through the pupil, raising the temperature of the tumor to 45–60°C, resulting in vascular occlusion and tumor necrosis in the tumor. The maximal penetration depth of TTT is 4 mm. It is suitable for small tumors with a thickness of <4 mm that are located outside the optic disc and macula or local recurrence after vitrectomy of the entire tumor. It is more effective for choroidal melanoma with a thickness of <2.5 mm. Tumors with a thickness > 3 mm should be treated with patch radiation therapy combined with TTT, that is, "sandwich" therapy. The advantages of TTT include the precise focus of the laser, which can cause immediate necrosis of the tumor and less damage to the surrounding normal choroid. It is easy to operate. The treatment can be completed in an outpatient clinic, and the treatment can be repeated. The disadvantage of TTT is that it is more likely to recur, and potential complications include occlusion of epiretinal membrane and branch retinal vein, retinal stretch, and secondary rhegmatogenous retinal detachment.

7.4 Photodynamic therapy (PDT)

PDT is a non-thermal laser that activates a photosensitizing dye (verteporfin) to induce vascular closure, tumor necrosis, and cell apoptosis, and can be used to treat small choroidal melanoma [55]. However, tumor pigmentation can affect the effectiveness of PDT, so PDT is mainly used in the treatment of small amelanotic choroidal melanoma, adjuvant treatment of radiotherapy, and supplementary treatment after radiotherapy failure.

7.5 Local tumor resection

Local tumor resection was first used for the residual tumor after radiotherapy, and later it was also reported as the first choice for the treatment of UM [56]. There are two types of surgery to remove the entire tumor through an incision in the sclera (excision) and to remove the entire tumor through the vitreous (endectomy). External resection is suitable for iris, ciliary body, and peripheral choroidal melanoma; internal resection is suitable for choroidal melanoma located retroequatorially. Local tumor resection can provide fresh tissue samples for histopathological diagnosis and genetic testing, and preserve the eyeball and vision. During local excision of the tumor, if there is residual tumor on the scleral surface or the tumor is close to the edge of the surgical resection area, radiotherapy can also be supplemented to prevent tumor recurrence. The effect of local tumor resection is usually ideal, but it is difficult and requires high surgical experience and technical requirements for the surgeon.

At present, the routine surgical indications for clinical UM local resection: (a) The maximal diameter of the tumor base is ≤15 mm; (b) the tumor has no local invasion,

or involvement of the sclera and orbit; (c) the tumor has no systemic metastasis. Contraindications to surgery: (a) extraocular invasion or distant metastasis of the tumor; (b) general conditions that cannot tolerate surgery; (c) flat diffuse tumors. The main complications of local tumor resection include retinal detachment, proliferative vitreoretinopathy, and hemorrhage.

7.6 Enucleation

Enucleation is required for large and advanced UM (maximal diameter of tumor base >20 mm or thickness > 12 mm), optic nerve involvement or orbital involvement, and/or secondary glaucoma [57].

7.7 Removal of orbital contents

For UM that invaded the orbit, orbital content extraction was used, and the eyelids were preserved as much as possible during the operation to facilitate rapid healing.

7.8 Immunotherapy

In recent years, with the rapid development of immunotherapy, the tumor microenvironment plays a pivotal role in cancer progression and treatment response. A study of the UM tumor microenvironment based on a public database found that people with high-risk UM risk scores were more sensitive to anti-programmed death receptor 1 immunotherapy [58]. Prostaglandin endoperoxide synthase can be used as an immunotherapy target for UM, and its inhibitor, celecoxib, can effectively inhibit UM cell growth and promote tumor cell apoptosis [59].

8. Prognosis

The 20 to 50% of patients with UM eventually die of tumor metastasis. Tumors metastasize through the blood circulation, with the liver taking the first place (64.86%), followed by the skin, stomach, lung, and bone.

Factors affecting the prognosis of patients with UM include: (1) Patient age. Those over 50 years old have a poor prognosis, which may be related to their reduced immune function. Reduced immune defenses in patients may contribute to tumor metastasis. (2) The largest basal diameter of the tumor. The prognosis of tumor base diameter ≤ 12 mm is better than that of >12 mm. The larger the tumor base, the greater the possibility of destroying blood vessels, the greater the contact area with the sclera, the greater the possibility of spreading outside the eyeball, leading to an increased risk of tumor metastasis. (3) The maximal height of the tumor. The prognosis of tumors whose maximal height exceeds 12 mm is significantly worse than that of those less than 12 mm. (4) The location of the tumor. If the front edge of the tumor is located in front of the equator, the prognosis is worse than that in the back of the equator; if the tumor invades the ciliary body further forward, the prognosis is even worse. (5) With or without ball spread. If the tumor invades the scleral duct and scleral wall tissue, its prognosis is poor. (6) Tumor cell type. Cell type is the most important factor influencing the prognosis of UM. The prognosis of the spindle cell type is better, and the prognosis of mixed cell type and epithelioid cell type is poor. Small tumors are often of spindle cell type, while epithelioid and mixed types are dominant in large tumors.

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