Guideline

Guidelines for the clinical diagnosis and treatment of retinoblastoma (2025)

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ABSTRACT

Retinoblastoma (RB) is the most common intraocular malignant tumor in children under five , which compromises the visual function and life of children. Since most RB patients have reached the extraocular stage at the time of initial diagnosis, the mortality rate remains high, which brings great challenges to clinical treatment. Therefore, early diagnosis and standardized treatment are of great significance for RB. To this end, the Ophthalmology Committee of the Ophthalmology Branch of the Chinese Medical Doctor Association, the Ophthalmology Committee of the International Intelligent Medical Association and the Ophthalmology Committee of the International Association of Translational Medicine presided over the formulation of the clinical diagnosis and treatment guidelines for retinoblastoma, which gave a detailed introduction to the etiology, diagnosis, staging and treatment of RB, aiming to help clinicians improve the diagnostic efficiency and formulate diagnosis and treatment plans for patients more quickly and effectively.

BACKGROUND AND METHODOLOGY

Retinoblastoma (RB) is the most common intraocular primary malignancy in children, mostly occurring in children under 5 years of age, with an incidence of 1/20000-1/15000. In recent years, significant progress has been made in the treatment of RB, but due to the limited medical resources and the difference in diagnosis and treatment levels in different regions at home and abroad, the current survival rate of RB patients is low, and the eye preservation rate is low, so it is necessary for the majority of ophthalmologists, pediatricians, and oncologists to pay attention to the standardized treatment of RB in order to achieve the best treatment effect.

Based on a series of problems existing in the diagnosis and treatment of RB, the Ophthalmology Special Committee of the Ophthalmology Branch of the Chinese Medical Doctor Association, the Ophthalmology Professional Committee of the International Intelligent Medicine Association, and the Ophthalmology Professional Committee of the International Translational Medicine Association organized ophthalmology clinical medical experts and ophthalmic clinical imaging experts to establish the "Retinoblastoma Clinical Diagnosis and Treatment Standard Guidelines (2025)" (hereinafter referred to as the "Guidelines") writing group in December 2023 , and held offline and online meetings according to the actual domestic situation and with reference to foreign advanced experience. After the first draft is formed, the experts will independently read and propose amendments by email and WeChat, and submit them to the core members of the "Guidelines" writing team, and the revisions will be sorted out and discussed and summarized through WeChat, email and online meetings, and the "Guidelines" will fully accept the suggestions and guidance of the participating experts

during the revision period, and finally reach the final draft of the "Guidelines", which lasted more than one year. The purpose of this article is to improve the diagnosis and treatment of RB among medical workers, and to provide a reliable treatment reference for those affected by RB.

DEFINITION OF RB

RB is a malignant tumor that occurs in the eye of children and originates from retinal photoreceptor precursor cells. Trilateral Rb refers to the development of a primary tumor in the sella or pineal gland in a patient with bilateral RB [1]. Bilateral Rb has tumors in both the pineal gland and sellar region, terming quadrulateral Rb[2].

EPIDEMIOLOGY

There are few significant differences in the incidence of RB in terms of region, gender, ethnicity, and eye distinction, but the survival rate and eye conservation rate vary greatly between regions due to economic conditions and medical standards. RB is divided into hereditary (40%) and non-hereditary (60%). Unilateral RB accounts for approximately 75 percent of cases, with onset occurring at two to three years of age, and bilateral RB at an earlier age [3]. The mean age at diagnosis for RB is 23.5 months globally, 14.1 months for RB in high-income countries (HIC), and 30.5 months in low- and middle-income countries (LMIC). In HIC, 98.5% of cases had intraocular RB, 1.5% had extraocular RB, and only 0.3% had systemic metastases. In LMIC, 49.1% of children had extraocular metastases and 18.9% had systemic metastases. The HIC survival rate is 100 percent, compared to only 57.3 for LMIC [4].

ETIOLOGY AND PATHOGENESIS

The occurrence and development of RB are closely related to genetic, epigenetic and environmental factors. In 1971, Alfred Knudson discovered the first tumor suppressor gene RB1 and proposed the " two-hit hypothesis" [3], that is, the first mutation occurs in germ cells and the second mutation occurs in somatic cells. In 1986, Friend et al. cloned the first human tumor suppressor gene RB1 for the first time, which was based on an in-depth study of RB, which finally determined that the RB1 gene was located on the long arm of chromosome 13 and the direct association between the RB1 gene and RB. RB is primarily caused by inactivation of the RB1 biallelic [5]. With the application of whole-genome testing technology, studies have found that most RB genetic abnormalities are far more than a "second hit" [6]. In a small number of children without RB1 gene abnormalities, abnormal expression of genes such as MYCN is also an important factor in the development of RB [7]. Among them, chromosomal fold increases in chromosomes 1q, 2p, and 6p, and chromosome deletion in chromosome 16q are common in RB [8]. It is worth noting that an increase in chromosome fold 2p can lead to an increase in MYCN gene expression, which is the main chromosome aberration in RB development. In addition, fold increases on chromosomes 1q and 6p can also promote oncogene expression and accelerate RB [6].

In recent years, epigenetic regulation has been found to play an important role in RB pathogenesis, such as abnormal DNA methylation, abnormal RNA and histone modifications, and chromosomal conformational changes [9]. Other factors such as environment are also associated with RB, such as radiation exposure, human papillomavirus infection, in vitro fertilization, etc.

TYPING OF RB

4.1 Classification according to genetic characteristics

(1) Hereditary RB: It is more likely to develop binocular or monocular multifocal RB, and only about 15% of them are unilateral [10]. There is also a correspondingly increased risk of developing other tumors, such as pineal blastoma, osteosarcoma, melanoma, and other malignant tumors[11] 。 (2) Non-hereditary RB: It is mostly unilateral, and the probability of other non-ocular tumors or inheritance to offspring is very low [10].

RBs can be classified into four distinct types, based on the timing of the first RB1 gene mutation [12]. (1) Familial hereditary type: The first RB1 gene mutation in this type comes from the parents and has a family history[13]Abramson DH, Gombos DS. The topography of bilateral retinoblastoma lesions[J]. Retina, 1996, 16(3): 232-239. ; (2) Isolated hereditary type: children often present with bilateral RB without family history, and the first RB1 gene mutation in this type comes from germline mutations before the formation of fertilized eggs [14]; (3) Chimeric type: This type of child has a unilateral onset, caused by a mutation in the RB1 gene after the formation of a fertilized egg, Heritability the child's germ cells are involved [15]; (4) Non-hereditary: RB1 gene mutations occur in somatic cells, often manifesting as unilateral sporadic lesions without genetic tendencies [16].

In addition to children with familial RB, the genetic status of isolated and chimeric RB is difficult to judge through clinical manifestations, so genetic testing and genetic counseling for children and their parents are effective means to improve the early detection rate of RB.

4.3 Classification according to the results of B-ultrasound examination

(1) Endophytic: the mass protrudes into the vitreous cavity, and the tumor cells cause vitreous implantation; (2) Exophytic type: the mass grows in the direction of the choroid, which can be accompanied by retinal detachment; (3) Mixed growth type: the lump has the characteristics of both endogenous and exophytic type, which is the most common type; (4) Diffuse infiltrating growth type: diffuse thickening of the retina.

4.4 Classification according to pathological characteristics

(1) Differentiated type: tumor cell nuclei have different morphologies and sizes, deep nuclear staining, and more common nuclear divisions. The nucleus can be seen in the F-W chrysanthemum-shaped cluster (Flexner-Wintersteiner rosette), which is a columnar or high columnar tumor cell centripetal neatly arranged into a wreath, the middle of the wreath is a hollow cavity, the inner wall of the cavity has an inner boundary membrane, and the nucleus is mostly located at the base of the outer side of the cytoplasm, forming a cross-section hollow papillary structure arrangement. In addition, the H-W chrysanthemum (Homer-Wright rosette), a pseudochrysanthemum-shaped mass, has no central cavity or visible blood vessels (Figure 1). (2) Undifferentiated type: common H-W pseudochrysanthemum-shaped mass, vascular growth around the tumor, with necrosis and calcification.

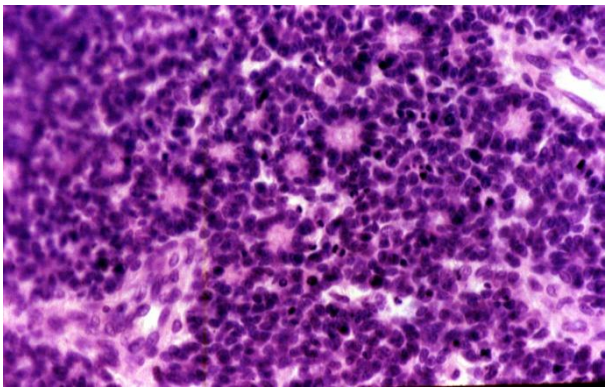

Figure 1 Histopathology of retinoblastoma (HE × 400).Low columnar tumor cells arranged in circles, presenting a "pseudorosette" pattern.

Diagnosis of RB

5.1 Clinical manifestations

Because RB patients are often very young, it is difficult

to complain of their own condition, and they often seek medical attention because of abnormal ocular appearance. Leukocoria is the most common manifestation of RB, followed by strabismus, and some children have red eyes and decreased vision. The tumor continues to grow within the eye, and proptosis may occur. Exexophytic tumors grow subretinally to form masses, which can cause retinal detachment; Endogenous tumors protrude into the vitreous, which can cause vitreous opacity. Further growth of intraocular tumors can cause secondary glaucoma, corneal degeneration, intraocular hemorrhage, iris redness, etc. The early manifestations of RB are similar to those of Coats disease, permanent embryonic angiogenesis, retinopathy of prematurity, familial exudative vitreoretinopathy, and congenital , cataract and further investigations are required to distinguish them in addition to clinical manifestations.

5.2 Imaging examination

5.2.1 Fundus photography

Binocular indirect ophthalmoscopy can be used to show single or multiple raised lesions in the retina, which are gray and translucent at first, and the color changes to opaque white or yellow as the tumor grows, and the retinal blood vessels on the tumor surface dilate and hemorrhage. If the pupils are dilated enough before the examination and cannot cooperate with the physical examination, it is best to perform under general anesthesia.

5.2.2 Ultrasonography

Key points of diagnosis: (1) Tumor echo characteristics: (1) low-density shadow connected to the wall of the eyeball, when the mass is necrotic or bleeding, the echo in it is uneven (Figure 2); (2) about 80% of tumors can see "calcium spots" with sound shadows; (3) Secondary retinal detachment. (2) Color Doppler ultrasound performance: (1) intratumor probing and blood flow signals that continue with the central retinal arteries and veins; (2) The spectrum is characterized by the blood flow spectrum accompanied by the same arteries and veins as the central retinal arteries and veins, with high speed and high resistance. Ultrasonography showed no radiation damage and showed good intraocular soft tissue lesions and calcifications. However, it has limitations for detecting orbital extension or optic nerve invasion and depends heavily on operator skill.

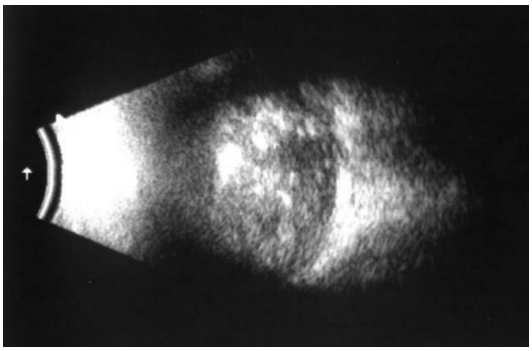

Figure 2. B-scan Ultrasound Image of Retinoblastoma.Irregular solid lesion within the vitreous, with heterogeneous internal echoes and detectable punctate hyperechoic foci.

5.2.3 CT

Key points of diagnosis: (1) Intraocular soft tissue density mass; (2) Flaky or clumpy calcification of the lump(Figure 3); (3) Moderate to significant enhancement of the enhanced scan mass; (4) There is no calcification in a small number of lesions, which needs to be diagnosed in combination with clinical symptoms, fundus examination and other imaging examination methods. (5) .Optic nerve thickening suggests tumor invasion(Figure 4).

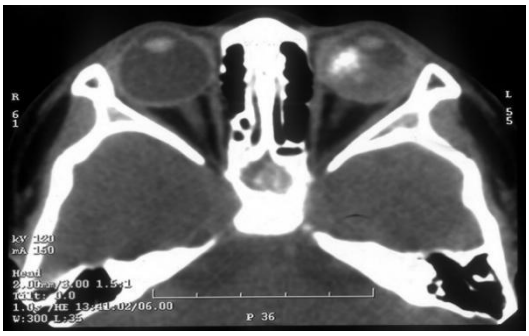

Figure 3. Axial CT Image of Left Eye Retinoblastoma.High-density mass with calcifications within the left eye.

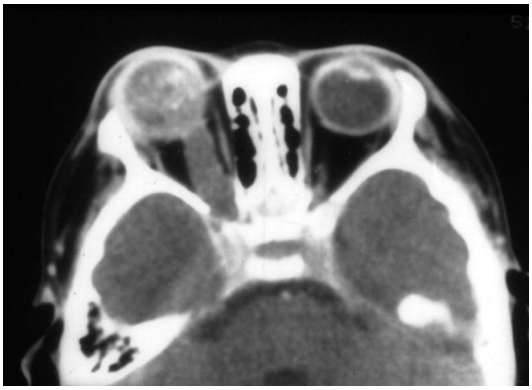

Figure 4 .Axial CT Image of Right Eye Retinoblastoma with Optic Nerve Extension.Soft tissue mass with punctate calcification within the right eye, thickening of the optic nerve, and tumor invasion of the middle cranial fossa.

5.2.4 MRI

Key points of diagnosis: :(1) Irregular, nodular intraocular lesion eyeball; (2) Compared with the normal vitreous, T1WI showed a slightly high signal, and T2WI showed a non-uniform low signal(Figure 5); (3) DWI showed that the tumor was hyperintense, and the ADC diagram showed low intensity; (4) Moderate or significant uneven strengthening after enhancement.

MRI is the best non-invasive test to evaluate retrobulbar tumor spread, optic nerve invasion, or intracranial spread without radiation damage. MRI is an essential imaging modality for pretreatment evaluation unless contraindicated, but MRI is not sensitive for calcifications.

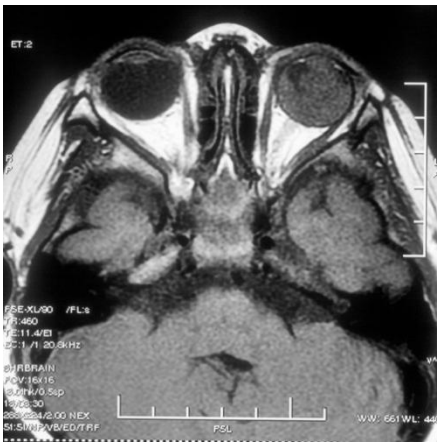

Figure 5.Axial MRI Image of Left Eye Retinoblastoma.Abnormal soft tissue signal within the vitreous cavity of the left eye, appearing isointense signal on T1WI with hypointense signal areas.

5.3 Histopathology

Histopathological examination (Figure 6) is the basis for diagnosis of RB and an important method to determine whether patients have histopathological high risk factors (HRF).

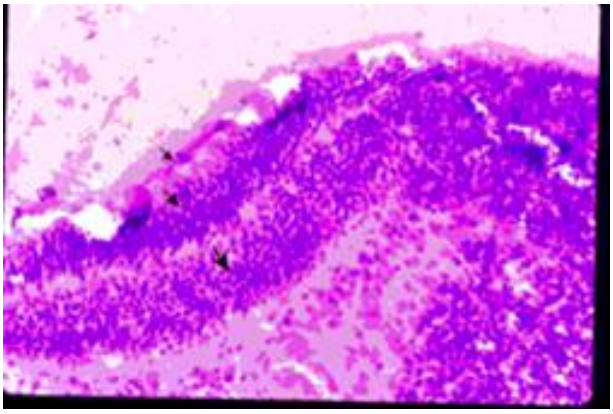

Figure 6 Histopathology of Retinoblastoma (HE × 200) The tumor originates primarily from the outer nuclear layer (large arrow) or inner nuclear layer (medium arrow) of the retina. The small arrow indicates the ganglion cell layer.

HRF is associated with intraocular recurrence and distant metastases [17], and in the presence of HRF, cerebrospinal fluid and bone marrow monitoring is required with adjunctive systemic chemotherapy [18]. HRF includes posterior optic nerve cribriform plate invasion, massive choroidal invasion, anterior chamber invasion, and scleral invasion.

5.4 Lumbar puncture inspection

RB can invade the optic nerve and cause intracranial dissemination, so lumbar puncture is indicated in patients with the following conditions to rule out CSF dissemination. (1) . Suspicion of optic nerve involvement beyond the globe on imaging (CT, MRI). (2) Identify patients in the extraocular stage and distant metastasis stage. (3) Pathology after enucleation suggests at least two risk factors.

5.5 Bone puncture examination

Children with recurrent or advanced RB, especially in the extraocular stage and distant metastases, should be confirmed for bone marrow invasion, and bone marrow aspirate for cytology is recommended.

STAGING OF RB

6.1 Intraocular retinoblastoma (IORB) staging

The two most commonly used staging methods for IORB

are the International Classification of Retinoblastoma (ICRB) and the International Intraocular Retinoblastoma classification (IIRC). There are two different versions of IIRC, namely the Los Angeles Children's Hospital version proposed by Linn in 2005 and the Philadelphia version released by Shields et al. in 2006, both of which divide intraocular stage RB into A~E for a total of 5 stages. Among them, ICRB is the most commonly used staging method in Indian studies [19].

6.1.1 ICRB staging

Stage A: Tumor diameter/thickness ≤ 3mm, away from vital tissues. Stage B: tumor diameter/thickness >3mm; or the tumor is ≤ 3mm from the macula; or the tumor is ≤ 1.5 mm from the optic disc, or the subretinal fluid is confined to within 3 mm of the base of the tumor. Stage C: C1: Subretinal implant tumor ≤ 3mm from the primary tumor; C2: Vitreous implant tumor ≤ 3 mm from the primary tumor; C3: Both are ≤ 3 mm from the primary tumor. Stage D: D 1: Subretinal implant tumor > 3mm from the primary tumor; D2: Vitreous implant tumor >3mm from primary tumor; D 3: Both are > 3 mm from the primary tumor. Stage E: Tumors make up more than 50% of the eyeball; or neovascular glaucoma; or anterior chamber, vitreous, subretinal hemorrhage; or tumor invasion into the optic nerve, choroid (>2 mm), sclera, anterior chamber, or orbit..

6.1.2 IIRC staging (Los Angeles Children's Hospital Edition)

Stage A (very low risk): small tumors scattered within the retina that do not pose a threat to visual function. All tumors were confined to the retina and ≤ 3.0 mm in diameter; The tumor was 3.0 mm from the macular > and 1.5 mm from the optic nerve >; There are no vitreous or subretinal implants. Stage B (low risk): No tumors implanted in the vitreous or subretina. Excludes tumors of stage A size and location; The subretinal fluid is confined to within 5.0 mm of the base of the tumor. Stage C (moderate risk): disseminated tumors with focal subretinal or vitreous implantation and various sizes and locations. vitreous and subretinal implant tumors are small and localized; Intraretinal disseminated tumors of various sizes and locations; Subretinal fluid is confined to 1 quadrant. Stage D (high risk): Diffuse vitreous or subretinal implantation. diffuse intraocular growth of the tumor; Extensive vitreous implantation in the form of oil; Subretinal implantation in the form of plates; Retinal detachment extends beyond 1 quadrant. Stage E (very high risk): with any 1 or more of the following characteristics. irreversible neovascular glaucoma; Massive intraocular hemorrhage; aseptic orbital cellulitis; The tumor reaches anterior to the vitreous; The tumor palpates the lens; diffuse infiltrating RB; Tabes dorsalis of the eyeball.

6.1.3 The 8th edition of the Cancer Staging Manual issued by the American Joint Committee on Cancer (AJCC) in 2017 for TNMH staging

Primary tumor (T):

cTX tumors cannot be assessed.

There was no evidence of tumor presence at cT0.

cT1 intraretinal tumor, the distance between the base of the tumor and the subretinal fluid ≤ 5.0mm;

cT1a tumor ≤ 3.0 mm in diameter and > distance from the macula and optic disc 1.5 mm;

cT1b tumor > 3.0 mm in diameter or 1.5 mm away from the macula and optic disc <.

cT2 intraocular tumors with retinal detachment, intravitreal implantation, or subretinal implantation;

The distance between cT2a subretinal fluid and the base of the tumor > 5.0mm;

cT2b tumors with intravitreal implantation or subretinal implantation.

cT3 intraocular advanced tumors;

cT3a eye atrophy;

cT3b tumors invade the flat part of the ciliary body, ciliary body, lens, suspensory ligament, iris, or anterior chamber;

elevated intraocular pressure cT3c with iris neovascularization and/or bull's-eye;

cT3d anterior chamber hemorrhage and/or massive vitreous hemorrhage;

cT3e aseptic orbital cellulitis;

cT4 extraocular tumors invade the orbit, including the optic nerve;

cT4a imaging evidence showing retrobulbar optic nerve involvement or optic nerve thickening, intraorbital tissue involvement;

Clinical examination of cT4b reveals significant proptosis and/or intraorbital mass

Regional lymph node metastases (N)

cNx stage: regional lymph node condition cannot be assessed
cN0 stage: no lymph node metastases were found
cN1 stage: regional lymph node metastasis
Distant metastasis (M)
cM0 stage: no symptoms of intracranial or distant metastases
cM1 stage: distant metastases without histopathological confirmation
• Stage cM1a: Metastasis to distant sites (bone marrow, liver, etc.) based on clinical or imaging studies
• Stage cM1b: Imaging findings suggestive of metastases to the central nervous system, but not trilateral RBpM1: distant metastases with histopathologic evidence
• Stage pM1a: histopathological evidence of metastasis to distant sites (bone marrow, liver, or other)
• Stage pM1b: histopathological evidence of tumor metastasis to cerebrospinal fluid or central nervous system
Genetic trait H typing
HX: There is no evidence of a mutation in the RB1 gene
H0: Presence of normal RB1 allele
H1: bilateral RB, trilateral RB, family history of RB positivity, or detection of somatic RB1 gene mutations.

6.2 Extraocular retinoblastoma (EORB) staging

The International Retinoblastoma Staging System (IRSS) is used for EORB staging [20] as follows: Stage I: enucleation of the eyeball, complete resection of the tumor. Stage I: enucleation, small remnants in the following forms. A. Tumor involvement of extrascleral tissue B. Tumor involvement of the incision end of the optic nerve. Stage III: Localized expansion. A. Significant orbital disease B. Preauricular or cervical lymph node disease. Stage IV: metastatic disease. a. Bone, bone marrow, and/or liver, but not central nervous system (CNS). A1. Single lesion. A2. Multiple lesions. b. Involvement of the CNS with or without other local or metastatic disease. B1. Involvement of the optic chiasmatic anterior optic nerve. b2. CNS clumps. B3. Leptomeningeal disease.

TREATMENT OF RB

7.1 Principles of Treatment

With modern the treatment concept of RB and the improvement of patient requirements, the treatment for RB has shifted from saving children's lives to saving children's lives and preserving children's eyeballs and even vision, so as to improve the quality of life.

7.2 Intraocular RB treatment

7.2.1 Topical treatment
Local treatments can be used for small stage A and B tumors in IIRC, including cryotherapy, laser photocoagulation therapy, and pupillary thermotherapy.
7.2.1.1 Cryotherapy
Triple freezing of RB through the sclera using a cryohead (temperature below −90~−80 °C) resulted in the formation of ice crystals and protein denaturation in tumor cells, resulting in rupture and necrosis of tumor cells. Cryotherapy can be used alone to treat anterior retinal RB at the equator, and when the conjunctiva is opened, the cryophora can reach the peripheral retina at the posterior equator [21]. In addition, freezing can disrupt the blood-retinal barrier, which is conducive to drug penetration, and cryotherapy for RB before chemotherapy can improve the effect of chemotherapy Rare complications include transient conjunctival edema, transient retinal dissociation, and vitreous hemorrhage after cryotherapy in large tumors or tumors with a history of radiation therapy [22].
7.2.1.2 Laser photocoagulation therapy
Green lasers (wavelength 532 nm or 536 nm), infrared lasers (wavelength 810 nm), and far-infrared lasers (wavelength 1064 nm) are used to destroy tumor blood vessels, which are more widely used because of their greater penetration [23]. The laser probe has a penetration focus of 1~2 mm and is easy to damage the fovea and optic disc, so it is only suitable for the treatment of peripheral retinal RB with a diameter of ⩽1 optic disc diameter. During the treatment, the power is set at 1000~2000 mW, and the energy should not be too high, because the laser spot will hinder the penetration of the

laser into deep tissues, and the second is to avoid complications such as vitreous implantation, hemorrhage, and retinal detachment. The duration of photocoagulation was 1~2 s until the color of the tumor turned white by indirect ophthalmoscopy. Complications of laser photocoagulation include retinal dissociation, vascular occlusion, and preretinal fibrous hyperplasia [24].

7.2.1.3 Transpupillary thermotherapy

Infrared heating of tumors to 45~60 °C can induce tumor cytotoxicity, and this temperature can also prevent retinal vascular coagulation and necrosis. Hyperthermia alone has been successful in curing more than 90 percent of patients with a diameter of ⩽1.5 mm [25]. In addition, hyperthermia enhances the cytotoxicity of carboplatin [26]. The disadvantage of hyperthermia is that there is no temperature monitoring device, the power setting is completely empirical, the treatment duration is usually 5~30 min, and the tumor color whitening and surface microbleeding are good indicators. Complications of hyperthermia include iris atrophy with or without focal lens opacity, retinal fibrosis, retinal vascular occlusion, and rhegmatogenous retinal detachment [27].

7.2.2 Chemotherapy

7.2.2.1 Systemic chemotherapy

Systemic chemotherapy, also known as chemovolume reduction, is treated with intravenous chemotherapy drugs. At present, the most commonly used chemotherapy regimen is a combination of vincristine, carboplatin, and etoposide, i.e., VEC. Dosage for patients under 3 years of age: vincristine 0.05 mg IV bolus per kilogram of body weight on day 1, etoposide 5 mg IV per kilogram body weight on days 1 and 2; Carboplatin 18.6 mg intravenously per kilogram of body weight on day 1. Dosage for patients over 3 years of age: vincristine 1.5 mg/m^2 (body surface area) intravenous bolus (maximum 2 doses of 2 mg), day 1; Etoposide 150 mg/m^2 (body surface area) 2 intravenous infusion, days 1 and 2; Carboplatin 560mg/m^2 (body surface area) intravenous 2-pulse instillation, day 1. Generally, once every 3~4 weeks, a total of 4~6 times.

Systemic chemotherapy is effective in early retinoblastoma, but not in advanced tumors. Shields et al. [28] found that chemotherapy alone had a 1-fold higher tumor recurrence rate than other treatments (hyperthermia, cryotherapy, laser, etc.), so it is currently mainly used to reduce tumor volume and reduce the risk of tumor metastasis [29], and is only used as part of the treatment regimen. Complications that may occur with systemic chemotherapy include bone marrow suppression, hearing loss, drug resistance, etc., and serious adverse reactions may endanger the life of the child and affect the long-term effect. 7.2.2.2 Local chemotherapy

Local chemotherapy is an improved treatment to increase the effective concentration of the drug and reduce the occurrence of systemic side effects. At present, it is mainly administered locally through arteries, veins, and vitreous cavities.

7.2.2.2.1 Intra-arterial chemotherapy

In the early stage, chemotherapy drugs were injected into the carotid artery through catheter intervention, and later the drugs were injected directly into the ophthalmic artery after clinical improvement. Munier et al. found that 48 children with stage D retinoblastoma received systemic chemotherapy and intra-arterial chemotherapy, respectively, and intra-arterial chemotherapy had a higher eye-preservation rate than systemic chemotherapy and was more advantageous in the treatment of advanced retinoblastoma [30].

7.2.2.2.2 Periocular chemotherapy

Periocular chemotherapy is a type of treatment in which carboplatin is injected around the eye and is often used as adjuvant chemotherapy. Through periocular injection, the drug can quickly enter the vitreous cavity, the concentration is 6~10 times that of systemic intravenous injection, and can remain in the eye for several hours, which is suitable for bilateral D~E stage tumors and recurrent local tumors. Complications of periocular chemotherapy include edema and ecchymosis of the orbits and eyelids, lipoatrophy of the eyelids, strabismus due to muscle fibrosis, and optic nerve atrophy [31].

7.2.2.2.3 Intravitreal chemotherapy

The most commonly used intravitreal chemotherapy drugs are melphalan and topotecan (alone or in combination), which are still used as first-line agents. The advantage of intravitreal chemotherapy is that it can greatly increase the drug concentration and reduce the complications of periocular injection, but because retinoblastoma is very disseminated, this therapy was initially highly controversial, and some scholars believe that the injection behavior may increase the risk of tumor metastasis, and the associated risk is increased if repeated

injections. Subsequently, ultrasound-guided avoidance of tumors, subconjunctival injection of chemotherapy drugs and other methods were gradually used to reduce the risk of tumor metastasis, and condensation and other methods were added to treat the injection site if necessary. Tumor dissemination is the greatest risk of intravitreal chemotherapy, so before IvitC, anterior chamber puncture is required to reduce intraocular pressure, the puncture point is far away from the lesion, and the postoperative puncture site needs to be triple frozen and gently shake the eyeball for 30 seconds to make it evenly distributed throughout the vitreous cavity. Avoid rubbing the eyeball after surgery, and the risk of tumor spread is 0 to 0.08 percent under strict procedures [32].

7.2.2.2.4 Anterior chamber injection chemotherapy

Patients with anterior room implants have stage IIRC E for them. Anterior chamber spread is considered a persistent manifestation of RB, but it does not carry a high risk of metastasis and therefore should not be treated with systemic adjuvant intravenous chemotherapy [33]. In recent years, some scholars have tried to treat anterior implantation with anterior chamber injection chemotherapy and achieved good results. Under the microscope, a 30G needle was used to insert the needle into the transparent limbus, and melphalan 3~15ug was injected into the anterior chamber and the root of the iris; Before removing the needle, freeze and thaw 3 times in a row at the needle insertion site with a cryohead, and apply antibiotic eye ointment to cover the eye. The most common complication of anterior chamber chemotherapy is cataract [34].

7.2.3 Surgical treatment

7.2.3.1 Enucleation

Enucleation remains an important and effective treatment for children with a high suspicion of metastasis. Caution should be exercised during surgery to avoid tumor spread, and postoperative children still need to receive chemotherapy or radiotherapy to reduce the recurrence rate of tumors, and regular follow-up is required. Prosthetic eye implants should be performed after enucleation to reduce the impact of surgery on orbital bone development [35]. Pathological biopsy should be performed after enucleation, and the lesion should be removed as much as possible to reduce the risk of tumor metastasis. Enucleation of the eyeball adversely affects the child's visual acuity and appearance.

7.3 Treatment of extraocular RB

There is no unified treatment for extraocular RB in the international community, and a combination of surgery, chemotherapy and radiotherapy is often required.

7.3.1 Radiation Therapy

7.3.1.1 External beam radiation therapy (EBRT)

EBRT is a traditional treatment that uses charged particle beams to kill tumor cells and is a traditional treatment that preserves the eyeball and vision. However, because it may cause problems such as secondary tumors and developmental defects, it is generally not used as the first choice of therapy. EBRT is mainly used for extraocular RB, and when the tumor invades the orbit or there is local intracranial invasion, in addition to enucleation combined with systemic chemotherapy, adjuvant EBRT is required to kill the residual tumor. EBRT remains the treatment of choice for patients in the intraocular phase who have failed systemic chemotherapy or IAC in combination with topical therapy and intravitreal chemotherapy.

7.3.1.2 Scleral dressing

The radionuclides commonly used for scleral dressing, such as Go60, I125, Ru160, and Ir192, are a type of brachytherapy with minimal impact on the tissues surrounding the tumor [36]. Complications of scleral dressing include radiation-related eye disease, secondary glaucoma, and proliferative retinopathy, and these complications are often concentrated.

7.3.2 Surgical treatment

7.3.2.1 Orbital enucleation The tumor has penetrated the eyeball and grows into the orbit, the optic nerve canal is enlarged, etc., orbital content enucleation should be performed, and postoperative combined radiation therapy, but most of the prognosis is not good. This surgery will affect the appearance of the child, and the indications should be strictly controlled. Indications: Tumor involvement in the intraorbital segment of the optic nerve and infiltration through the eyeball into periorbital tissues.

7.4 Treatment of RB in metastatic phase

When only lymph nodes metastasize, lymph node

dissection surgery can be performed at the same time as the treatment of the primary tumor, and chemotherapy and radiotherapy can be adjuvanted. If metastases are distant by hematologic route, high-dose chemotherapy and autologous peripheral blood hematopoietic stem cell transplantation are indicated.

7.4.1 High-dose chemotherapy The main regimens of CEV and CE were used, and the dose was used in the high-dose group. If the tumor is in slow remission, regimens such as CTVCVVD/CVP can also be used. The total course of treatment is generally 48~52 weeks.

7.4.1.1 CTV regimen Carboplatin, teniposide and vincristine triple integrated medication, specific dose: carboplatin 18.6mg/kg or 560mg/m² (<10kg) a day, 600mg~700mg/m² (≥10kg), intravenous infusion on the first day (≥ 10kg can be administered in 2~3 days); Teniposide 3~9mg/kg a day (3mg/kg for <10kg, 9mg/kg for >10kg) or 230mg/m (>10kg), on the 1st ~ 2nd day (> 10kg children can be divided into 2~3 days), intravenous infusion; Vincristine 0.05 mg/kg (<10 kg) or 1.5 mg/m² (≥ 10 kg, maximum dose 2 mg) intravenous bolus or infusion on day 2.

7.4.1.2 CV regimen cyclophosphamide and vincristine dual integrated medication, specific dose: cyclophosphamide 65mg/kg, intravenous 393 pulse infusion on the 1st~2nd day (the total amount can be divided into 4 days of intravenous infusion for children with <10kg), mesna rescue, 60mg/kg (cyclophosphamide should be applied in 0, 4, 8h divided into 3 small pot infusions); Vincristine 0.05 mg/kg (<10 kg) or 1.5 mg/m² (≥ 10 kg, maximum dose 2 mg) intravenous bolus or infusion on day 1. It can be used interchangeably with CTV.

7.4.1.3 CVD/CVP scheme

Cyclophosphamide, vincristine and anthracycline drugs are triple integrated drugs, specific dose: cyclophosphamide 65mg/kg (<10kg) or 1.5g/m² (≥10kg), intravenous infusion on the first day, mesna rescue, 60mg/kg (cyclophosphamide is applied for 0, 4h, 8h in 3 small pot instillations), in order to reduce the toxicity and side effects, cyclophosphamide can be applied in 2-4 days (the rescue dose of mesna is 360~420mg/m each time, and cyclophosphamide is instilled into a small pot for 0, 4 and 8h).)。 Vincristine 0.05 mg/kg (< 10 kg) or 1.5 mg/m (≥ 10 kg, maximum dose 2 mg) intravenous bolus or infusion on day 1. Anthracyclines: (1) doxorubicin 30 mg/m2 (≥10 kg) or 1.2 mg/m² (<10 kg) a day, intravenous infusion for 30 minutes, day 1; (2) Pirarubicin 25mg/m (≥10kg) or 1.0mg/m (<10kg) a day, intravenous infusion for 30 minutes, day 1. It is used in the high-risk group and children with relapsed RB, with a cycle every 3 weeks, alternating with a high-dose VEC regimen.

7.4.2 Autologous peripheral blood hematopoietic stem cell transplantation

If bone marrow is not involved at baseline, it can be collected after either induction chemotherapy. If there is bone marrow metastasis, it should be performed after 2 courses of chemotherapy with minimal bone marrow residue turning negative. The main regimens of autologous peripheral blood hematopoietic stem cell transplantation pretreatment are as follows. (1) CEC regimen: carboplatin 250mg/m daily, intravenous infusion on days -8 to -4; Etoposide 350 mg/m² daily intravenously on days -8 to -4; Cyclophosphamide is given intravenously at 1.6 g/M daily on days -7 to -6. When the application of carboplatin and podophyl acetylin in the early stage of conventional chemotherapy is not effective, the following pretreatment regimen can be applied. (2) CTM regimen: carboplatin 250mg/m daily, intravenous infusion on days -6 to -4; Certepe, 200 mg/m/day, intravenous infusion on days -6 to -4; Melphalan is 160 mg/m daily on day -3, intravenous infusion. (3) BM regimen: busulfan, 3.2mg/m daily, -6 to -3 days, intravenous infusion or oral; Melphalan 120mg/m2 daily intravenous infusion on day -3. Twenty-four hours after stopping chemotherapy, granulocyte colony-stimulating factor was administered 5 ug/kg per day, subcutaneously or intravenously instilled into neutrophil ≥1.5x10/L.

FOLLOW-UP

Regular follow-up of children with RB is part of standardized treatment. Patients treated with eye conserving therapy will be reexamined once every 3~4 weeks after the first local treatment, and the examination and necessary repeat treatment will be performed under general anesthesia until the tumor completely regresses or calcification. If combined chemotherapy is required, the follow-up examination and ocular local treatment should

be arranged 1~3 days before each chemotherapy. After , control 1~3 months of reexamination will be arranged according to the situation, and if the tumor recurs or new tumor lesions appear, the treatment will be repeated until the disease is controlled. Follow-up visits every 3~6 months after enucleation surgery, and pay attention to the condition of the contralateral eye. It is generally believed that the condition can be considered cured when the condition is stable to 6~7 years old, and it can be rechecked at an interval of 6~12 months; After the age of 13, regular follow-up can be arranged every 2~3 years, and attention should be paid to the occurrence of secondary tumors in the soft tissues of the head, brain, skin and bones.

SUMMARY

The prognosis of RB depends on the extent of the tumor, the presence or absence of systemic metastases, and the approach to treatment. Patients with early detection and treatment, yield better outcomes and patients with advanced or metastatic RB have a worse prognosis. The care and treatment of RB requires a multidisciplinary approach, including paediatrics, ophthalmology, radiology, pathology, and genetic counseling. Early diagnosis and treatment are key to improving survival and reducing complications. In the process of diagnosis and treatment, the overall condition of the child should be fully considered and an individualized treatment plan should be formulated.

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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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