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INTEGRATED STUDY MASTER'S THESIS

Retinoblastoma: A comprehensive Review of Genetics, Diagnosis and Treatment

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1. Summary (Abstract)

Retinoblastoma is an uncommon yet highly aggressive pediatric ocular malignancy that predominantly affects those under the age of five. This thesis provides a comprehensive analysis of the disease, covering its genetic basis, clinical presentation, diagnostic methods, and treatment options. Relevant literature was selected through a focused review of scientific sources, based on language and relevance to retinoblastoma. (1)

In most instances, retinoblastoma results from mutations in the RB1 tumor suppressor gene, which leads to uncontrolled cell proliferation. (1), (2)

In most cases, retinoblastoma is caused by mutations in the RB1 tumor suppressor gene, leading to uncontrolled cell proliferation. A smaller subset involves MYCN amplification which is tied with more rapidly progressing tumors. The condition manifests in heritable and non-heritable forms, with heritable cases often being bilateral and carrying an elevated risk of secondary cancers. (1)

Early diagnosis is crucial for successful treatment, with a white pupillary reflex and misalignment of the eyes being frequently observed symptoms. Imaging techniques, including ultrasound and MRI, are essential in confirming the identification and assessing tumor extent. Staging systems such as the International Classification of Retinoblastoma (ICRB) guide treatment decisions. (1)

Treatment advancements, such as intra-arterial chemotherapy (IAC) and intravitreal injections, possess significantly improved eye preservation rates. However, survival rates remain uneven worldwide. (1), (2)

Key words: Retinoblastoma, RB1 gene, pediatric oncology, genetic mutation, leukocoria, intra-arterial chemotherapy, enucleation, trilateral retinoblastoma.

2. Introduction

Retinoblastoma represents a critical intersection of pediatric oncology, ophthalmology and genetics. As a malignancy originating from immature retinal cells, it poses diagnostic and therapeutic challenges due to its occurrence in infants/toddlers and its potential for devastating visual impairments and life-threatening consequences if untreated. The disease's molecular basis, rooted in the loss of RB1 tumor suppressor function, has made it a cornerstone model in cancer biology offering insights into cell regulation and hereditary

cancer syndromes. (1)

Despite being one of the most treatable childhood cancers when detected early, retinoblastoma outcomes reveal stark global inequities. In high income countries, advanced screening protocols and multimodal therapies achieve near normal life expectancy, whereas in resource limited settings, late presentation and fragmented care lead to disproportionately high rate of mortality. (2)

Clinically, retinoblastoma's hallmark signs leukocoria (white reflex in the eye) and strabismus (misalignment of the eyes) are common things found in retinoblastoma, are often missed in primary care, delaying referral. The evolution of classification systems (Reese-Ellsworth to ICRB) reflects progress in risk stratification, while treatment has shifted from radical enucleation to precision approaches like intra-arterial chemotherapy and target intravitreal therapies. However, these advancements are not universally accessible, and germline mutation carriers require life long surveillance for secondary malignancies. (3)

This thesis explores the tension between retinoblastoma's biological complexity and the practical realities of global care delivery. Through advancements of current evidence and a detailed clinical case, it examines how genetic insights, diagnostic refinements and therapeutic advances can be translated into equitable outcomes.

2.1 Aims and Objectives

The purpose in relation to this literature review is to offer an overview of present knowledge about retinoblastoma, including its genetics, clinical presentations, diagnosis and treatment. Additionally, this review seeks to focus on summarize and critically assessing recent advances in diagnosis and treatment, especially methods that preserve the eye and vision. Moreover, there is an emphasis on identifying knowledge gaps and challenges, and suggestions for areas for future research and improve care.

3. Literature search strategy and methodology:

Research for this literature review was carried out between November 2024 – May 2025. The primary databases used for sourcing information were PubMed, The National Cancer Institute (NCI) and EyeWiki. The main keywords used was "Retinoblastoma" Articles published in English were reviewed in full if their titles and abstracts indicated relevance, and those that provided relevant insights were included in the review.

Additionally, parts of this review were improved with the assistance of OpenAI's ChatGPT tool. The model supported the writing process by enhancing academic tone, highlighting spelling and grammar mistakes. (20)

4. Results

4.1 History

Retinoblastoma was first documented in 1597 by Peter Pawius, a Dutch anatomist, who performed an autopsy on a child with a large ocular tumor invading the orbit and brain. (4)

In 1805, William Hey, a British surgeon, introduced the term *fungus haematodes* to describe retinoblastoma as an ulcerating mass that disrupted the internal structure of the eye. This term was later replaced by Rudolph Virchow, a German pathologist, who named it *glioma of the retina* in 1854. Virchow's classification emphasized its glial cell origin. Building on Virchow's work, Hirschberg further classified these gliomas into exophytic and endophytic patterns. (4), (2), (20)

James Wardrop, a Scottish surgeon and ophthalmologist, classified the disease as a retinal tumor in 1809. Despite the limitations of microscopic tools, he traced its origin to the retina and pioneered enucleation as the definitive treatment, laying the groundwork for modern ophthalmic oncology. (2), (4), (20)

A significant histological breakthrough occurred in 1891 when Simon Flexner, an American pathologist, identified cellular rosettes within retinoblastoma tumors. Hugo Wintersteiner, an Austrian ophthalmologist, expanded on this discovery by describing the lumen structure of these rosettes. Their finding led to the classifications of these structures as Flexner-Wintersteiner rosettes, which are indicative of retinal differentiation within the tumor. These rosettes remain an important diagnostic feature in retinoblastoma pathology today. (4), (5)

4.2 Epidemiology

Retinoblastoma is a rare pediatric malignancy, with global incidence rates ranging widely from 3 to 40 incidence per million live births. Among children below 5 years old in the United States, it accounts for 6.1 % of all cancers in childhood. The disease typically develops in early childhood, most often between 3 and 5 years of age, with the highest incidence observed in children under 4. Retinoblastoma affects equally between females and males, with approximately 60% of instances with retinoblastoma appear unilaterally

(affecting one eye) at first, with the other 40% showing bilateral (affecting both eyes) involvement. The most prevalent presenting signs include leukocoria (white pupillary reflex) 60% and strabismus (misaligned eyes) 20%. (1), (2), (4)

A global study highlights striking differences in the age at diagnosis and access to follow-up care. The average age at diagnosis is 9 months in Europe, 12 months in Nort America, and 22 months in Asia. This delay is concerning, especially since Asia has the highest number of new cases annually, about 3,000 compared to 300 North America. (2), (3), (4)

These variations in early detection and access to care contribute to substantial differences in survival outcomes. In high-income countries, survival rate for retinoblastoma reaches nearly 97% due to timely diagnosis and access to treatments such as enucleation, radiotherapy and intra-arterial chemotherapy. However, in upper- middle-income regions, survival drops to 79%, and in low-income countries, it can fall as low as 40% primarily due to late diagnosis and lack adequate treatment. This disparity is illustrated in Figure 1, which highlights the global inequality in retinoblastoma survival based on socioeconomic status. (2), (20)

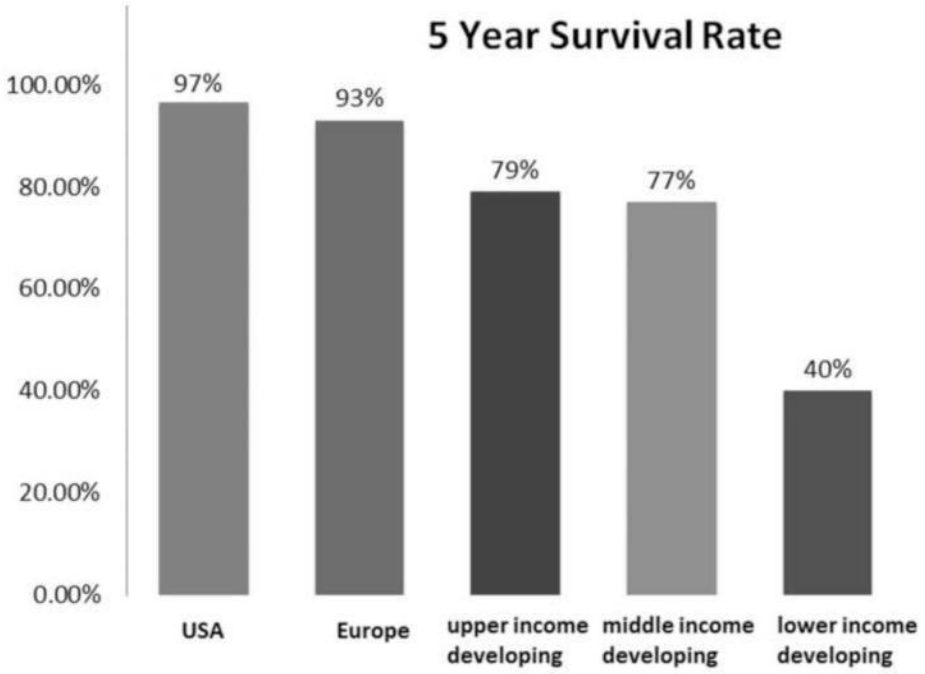

Fig 1 Survival rates for children with retinoblastoma over 5 years show significant variations across countries, largely due to differences in social economic conditions. In high-income nations like United states, the rate is close to 97%, while in low-income developing countries, it can be low as 40%. (2)

4.3 Clinical presentation and Patient assessment in Retinoblastoma

In the absence of screening, retinoblastoma is often first identified through visible ocular signs. One of the earliest and most recognizable signs is leukocoria, an abnormal white reflection from the pupil, often noticed by parents or caregiver in flash photographs (Fig2). This white pupillary reflex can indicate the presence of a tumor in the retina. Another common early sign is strabismus, or misalignment of the eyes, which may be the first indication of an underlying intraocular tumor (Fig.3). Both signs are important visual cues that should indicate immediate medical evaluation. (1)

Fig. 2 Leukocoria observed in a patient with retinoblastoma. (1)

Fig. 3 Strabisms observed in a patient with retinoblastoma. (16)

On uncommon occasions, retinoblastoma may present with pain and inflammation in the eye. These symptoms may resemble those seen in other eye conditions, such as eye infections inside the eye (endophthalmitis), inflammation of the inner the eye (uveitis), bleeding within the eye (hemorrhage) or infection of the tissue surrounding the eye (preseptal and orbital cellulitis).These symptoms often indicate that the tumor has extended beyond the eye which indicate a poor prognosis. (1)

Retinoblastoma has the potential for local infiltration, penetrating invading nearby tissues such as the eye's vascular layer (choroid) or its though outer membrane (sclera) and can extend along the optic nerve pathway right into the orbital space. Beyond local spread, this malignancy can also disseminate via the bloodstream, resulting in distant metastases. Common sites for hematogenous spread include the skeletal system, liver, central nervous system (CNS), and various other organs throughout the body. This capacity for both local invasion and distant metastasis underscores the aggressive nature of retinoblastoma and the critical importance of prompt identification and comprehensive management. (1), (20)

A thorough patient history is essential in the assessment of suspected retinoblastoma. Family history is particularly important, as children of individuals with heritable retinoblastoma have 50% risk of inheriting the genetic change, with those who inherit the mutated allele facing a 90% risk of developing the disease. The presence of other malignancies in the family, particularly sarcomas, should also be noted. Parents should be specifically asked if they noticed a white reflection in their child's eye or any misalignment of the eyes, as these may be early signs of retinoblastoma. It is important to document the time of onset of leukocoria, since delays in referral can worsen invasive treatments. Any previous examinations or diagnostic test should be collected and review to support the diagnostic process. (1)

The clinical examination should begin with age-appropriate visual acuity testing for each eye, followed by a detailed ophthalmologic examination. This includes a physical examination of the eyes, assessing for external signs such as proptosis (forward displacement or bulging of the eye), periorbital swelling, or evidence of cellulitis (inflammation or infection of the soft tissues around the eye, often appearing as redness, warmth, and tenderness). (1), (2), (3)

A sit lamp examination, a test using a specialized microscope that projects a thin beam of light into the eye, is used to inspect the anterior segment in detail. During this exam, signs to look for include for ciliary injection (redness around the cornea), pseudohypopyon (white tumor cells layering in the front chamber), iris neovascularization and signs of secondary glaucoma, all of which may indicate tumor-related complications. (1), (2), (3)

Testing the pupillary reflex is important to rule out an afferent pupillary defect, which may indicate unilateral or asymmetric dysfunction of the anterior visual pathway, a characteristic finding in advanced intraocular tumors such as retinoblastoma. (1), (3)

4.4 Pathology and Histopathology

Retinoblastoma is complex ocular malignancy that originates from neuroectodermal cells in

the inner layer of the optic cup. This tumor typically manifests as a multilobulated white mass, capable of growing towards the vitreous or subretinal space, forming vitreous or subretinal seeds. As it develops, the tumor creates sleeves and cuffs around central blood vessels, which serve as its primary source of nutrition. The growth pattern of retinoblastoma can vary, including diffuse growth within the retina itself, with nutrition derived from the retinal vasculature. These seeds are avascular and have necrotic regions in the middle that are separate from the vitreous or subretinal fluid. (2), (3), (20)

Due to its rapid growth, the tumor has a tendency to undergo ischemic necrosis when it exceeds the limits of its blood supply, at a distance of 90-110μm from the central vascular channel. This may result in areas of the tumor exhibiting dystrophic calcification, producing a distinctive curdled or crumbly white appearance on gross examination (Fig.4), (2). These necrotic and calcified areas are frequently accompanied by marked anaplasia, characterized by enlarged, hyperchromatic nuclei and atypical miotic figures, which reflect a high-grade, aggressive tumor phenotype with increased metastatic potential. Calcium deposition is frequently prominent in eyes that have previously undergone radiotherapy or chemotherapy. (19), (6)

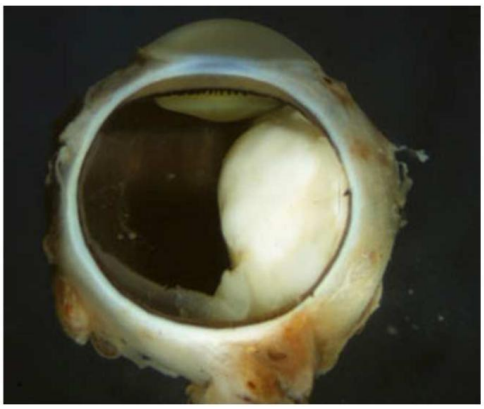

Fig. 4 Macroscopic examination of retinoblastoma (2)

A key aspect of retinoblastoma's microscopic analysis is the evaluation of tumor differentiation, which is primarily based on the rosettes. These rosettes are circular arrangements of tumor cells that indicate varying degrees of differentiation; well differentiated (>50% known as Homer-Wright rosettes) or poorly differentiated (<50% known as Flexner-Wintersteiner rosettes) (Fig.5, Fig.6). In some cases, especially in retinocytoma, fleurettes , a distinct cellular arrangement, are present and often contain areas of calcification, indicating a higher degree of differentiation (Fig.7). (6)

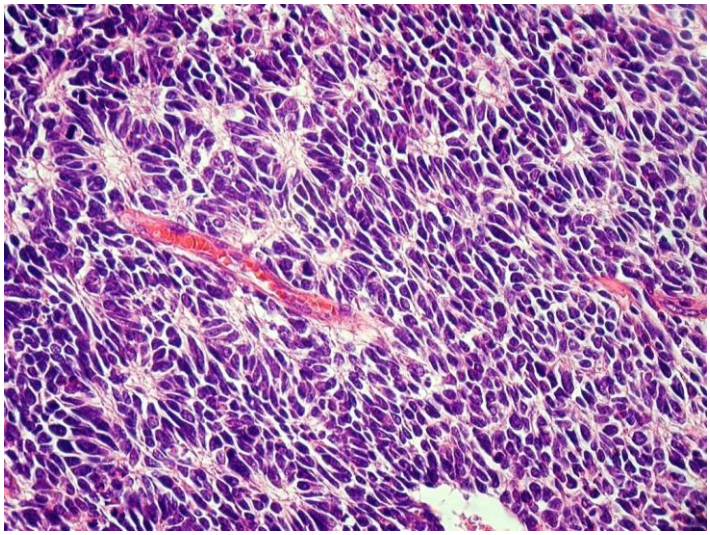

Fig. 5 Homer Wright rosettes (3)

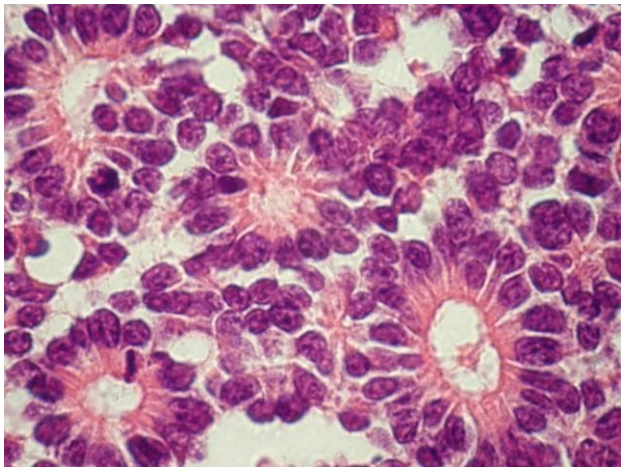

Fig. 6 Flexner-Wintersteiner rosettes (3)

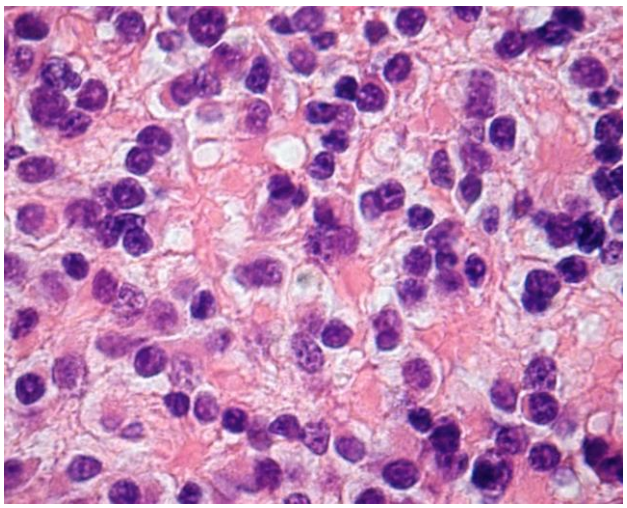

Fig. 7 Fleurettes (3)

Post-enucleation assessment of retinoblastoma focuses on identifying specific high-risk

factors indicate an increased potential for metastasis. These histopathological high-risk factors (HRFs) include extensive choroidal infiltration, infiltration of the optic nerve past the lamina cribrosa, the presence of tumor at the optic nerve resection edge and involvement of the iris, ciliary body, sclera, and extraocular tissue infiltration. The significance of these HRFs lies in their role in estimating the risk of orbital recurrence and metastatic spread. (6)

Survival outcomes differ significantly based on the extent of optic nerve involvement, with rates exceeding 90% for prelaminar involvement, dropping to 85% for laminar, 60% for post-laminar and just 35% when the surgical margin is affected. For cases with widespread choroidal invasion, the overall survival rate is approximately 70%. (2)

Identifying these high-risk features (HRF) is essential for guiding treatment decisions. In cases where HRFs are present, systemic adjuvant chemotherapy is often recommended to lower the chance of disease progression and improve survival outcomes. (6) A study examined 80 surgically removed (enucleated) eyes with one sided (unilateral) retinoblastoma and histological features associated with increased risk, compared outcomes between patients who received adjuvant therapy after enucleation (46 patients) and those who did not (34 patients). The results revealed a significant reduction in metastasis rates in patients exhibiting extensive choroidal infiltration or retrolaminar optic nerve invasion, with only 4% of the treated group developing metastases compared to 23% in the untreated group. Notably, massive choroidal invasion carries a higher risk of metastasis when combined with optic nerve involvement, whereas isolated choroidal invasion shows no significant risk. (7)

The evaluation of these factors allows clinicians to estimate the likelihood of orbital return and metastasis, ultimately informing the decision to implement additional systemic therapy to enhance survival prospects in high-risk cases. (6)

4.5 Genetic Basis

Retinoblastoma arises due to mutations in the RB1 gene, a tumor suppressor located on chromosome 13q14. RB1 encodes the retinoblastoma protein (pRB), which have a critical role in regulating cell cycle progression by binding to and inhibiting E2F transcription factors, thereby blocking the transition from G1 to S phase. When pRB is damaged or lost resulting from mutations in the RB1 gene, this control is disrupted, leading to unchecked cell division and tumor formation. (1), (8)

This process follows Knudson's "two-hit" hypothesis, which indicates that the two alleles of the RB1 gene have to be inactivated for tumorigenesis to occur (Fig.8). The first hit may be

germline (inherited), meaning the mutation is present in the egg or sperm, and can be passed on to offspring. The second hit is typically Somatic (acquired) occurring in a single cell during an individual's life and not inherited. Bot hits result the complete of functional pRB, which disrupts normal cell proliferation and genomic stability, contributing to tumor development. (2)

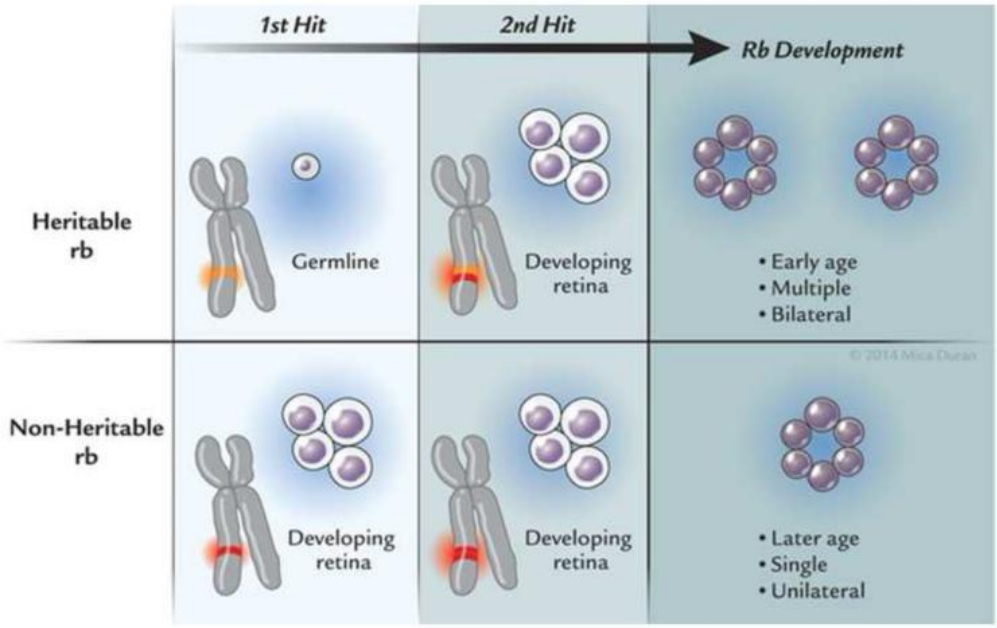

Fig 8. Inheritance of Retinoblastoma, a germline mutation combined with a somatic second hit leads to early onset, bilateral, and multifocal tumors. In non-heritable cases, both mutations occur somatically in the retina, resulting in later-onset, unilateral and typically single tumors. (2)

Approximately one-third of retinoblastoma cases are heritable, characterized by a germline mutation in one RB1 allele. This mutation exists throughout all cells of the body and follows an autosomal dominant inheritance pattern with high penetrance (90%). These patients often develop bilateral and multifocal malignancies and are at increased chance of secondary malignancies, such as trilateral retinoblastoma, involving pineal or suprasellar primitive neuroectodermal tumors. (1), (8)

The remaining two-third of cases are unilateral retinoblastoma without a familial history is typically considered non-heritable. These cases usually involve two somatic mutations occurring in retinal cells. Although they are less likely to be inherited, approximately 15% of unilateral cases still carry germline RB1 mutations. As such, comprehensive genetic testing is recommended for all patients. Non- heritable retinoblastoma typically presents as unilateral

and unifocal, and patients with no germline mutation have substantially lower, approximately 1% risk of transmitting disease to their offspring. (1)

A rare subset (<2%) of retinoblastoma cases develops without RB1 mutations is instead driven by MCN amplifications. MYCN, part of the MYC gene family, encodes a transcription factor essential for embryonic cell proliferation and differentiation. In these cases, high MYCN expression promotes aggressive tumor behavior. (11), (12)

Tumors with MYCN amplifications and intact RB1 tend to be unilateral, poorly differentiated, and more likely to metastasize. These tumors often exhibit resistance to standard chemotherapy and present distinct gene expression profiles. While rare, identifying MYCN – driven retinoblastoma is essential for tailoring management strategies. (12)

4.6 Retinal development and the cellular origins

Retinal development follows a regulated sequence that begins early in embryogenesis and continues through the late fetal stages. It originates from the neuroectoderm, forming the optic vesicle, which gradually gives rise to the mature retinal layers. Retinal cells emerge in a specific order: neuroepithelial cells form first, followed by photoreceptors and ganglion cells, with horizontal, bipolar and amacrine cells appearing later. (2), (12)

Disruptions in this developmental process can lead to retinoblastoma. Research has shown that the tumor does not always originate from the same retinal cell type, instead, it can arise at a different stage of development. This helps explain the variation in tumor behavior, morphology, and response to treatment. Based on gene expression profiles, at least three molecular subtypes of retinoblastoma have been identified, each potentially reflecting a different point of origin within retinal development (Fig.9). (2), (12)

The first group seems to develop from early retinal progenitor cells (RPc). These tumors tend to be poorly differentiated and exhibit more more aggressive behavior, with an increased risk of spreading beyond the eye including into the optic nerve or surrounding tissues. The second group is believed to originate from cone photoreceptor cells. This tumor tends to be better differentiated, often displaying structures like Flexner-Wintersteiner rosettes (which are a hallmark of retinal cell development), and tend to follow a less aggressive clinical course. These tumors usually grow in a more organized way and may have a less aggressive clinical course. The third group shows a hybdrid gene expression profile, containing markers from

both rod and cone cells. This suggests a mixed or intermediate cell of origin, and these tumors closely resembles normal retinal tissue. (2), (12)

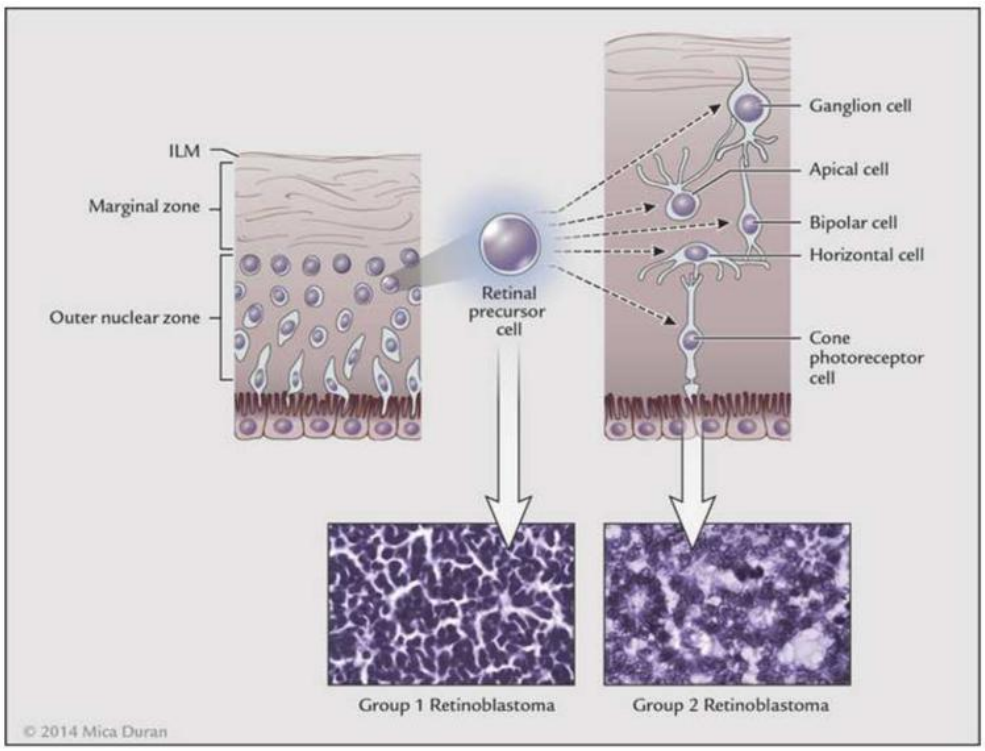

Fig. 9 Gene expression profiling (GEP) suggests retinoblastoma originates from primitive retinal precursor cells (RPCs) in the developing retina's outer nuclear zone. Early mutations lead to Group 1 retinoblastoma, which retains RPC gene expression. Later mutations result in Group 2 retinoblastoma, which show differentiation into cone photoreceptor, including rosette and fleurette formation. (2)

4.7 Screening and early detection

According to the American Academy of Pediatrics policy report, red reflex examinations should be conducted on all neonates, infants, and children prior to leaving from the neonatal unit and during each subsequent routine health checkup. The red reflex test is conducted in a darkened or dimly lit environment using either a direct ophthalmoscope or a retinoscope. The examiner positions the instrument approximately 30-45 cm away from the patient's eyes, a distance that optimizes the visualization of the red reflex while minimizing obstruction from the eyelash or eyelids. When the pupils are exposed to the light at this distance, they should appear symmetrically red-orange in both eyes under normal conditions. Leukocoria, which appears as white or pale reflection instead of the normal red reflex, is the most frequent initial sign of retinoblastoma. (1), (3)

Regular screening of newborns and siblings of individuals diagnosed with retinoblastoma is crucial, since ongoing eye examinations during childhood facilitate early detection of the disease. Families with a history of retinoblastoma are advised to seek genetic consultation, which provides important information about the risk of the disease occurring in other family members. For individuals considering having children, genetic testing for mutations in the RB1 gene is strongly recommended. (1), (3)

Retinoblastoma is passed down through an autosomal dominant manner. If one parent carries a mutated RB1 allele, their child has a 45% chance of inheriting this mutation. Preimplantation genetic testing is a part of early prenatal screening, which also includes both early and late prenatal testing. Preimplantation genetic testing is performed alongside in-vitro fertilization (IVF), enabling detection of mutant RB1 alleles prior to embryo transfer. This approach allows partners to choose an embryo that do not carry the inherited mutation for implantation. A non-invasive test, Cell-free fetal DNA (cffDNA) testing, might be conducted as early as the eight week of pregnancy and provides a conclusive diagnosis. The presence of RB1 mutant alleles is detected by isolating fetal DNA from placental trophoblasts found in maternal blood samples. Invasive prenatal diagnostic techniques include amniocentesis and chorionic villi sampling (CVS), has the potential to be carried out during the second trimester. In order to collect the placental tissue or amniotic fluid, separately, a needle is inserted trans-abdominally into the uterus during CVS and amniocentesis under ultrasound. (1) (2)

Trans-cervical technique is another method that may be performed. Many families may postpone the prenatal testing due to the possibility of miscarriage, bleeding, infection, rupture of membranes or inconclusive outcomes. Fetal ultrasound or MRI may be used for late prenatal screening, although only RB1 can be confirmed if it is visible in utero. (1), (3)

Early detection of RB1 mutations makes it possible to monitor the pregnancy more closely, plan the timing of delivery, and start treatment shortly after birth. This can greatly improve the child's chances of better outcome and may help to saving the affected eye and vison. (1), (3)

4.8 Diagnostic Methods

The diagnosis of retinoblastoma is confirmed through a combination of clinical examination and imaging techniques. The initial and most critical step is a detailed assessment of the ocular fundus, often carried out under anesthesia to allow for maximal pupil dilation and optimal visualization, especially in young children. Fundoscopy enables the clinical to

directly visualize intraocular tumors, asses their number, size, location and evaluate for signs of vitreous or subretinal seeding. This examination also allows for the identification of characteristic tumor features. Retinoblastoma typically appears as white or cream-colored, often accompanied by increased vascularization. The three main growth types of retinoblastoma expansion are endophytic, exophytic and diffuse infiltrating. (3)

In addition to imaging and clinical evaluation, genetic testing using RB1 gene sequencing is crucial in confirming the diagnosis and determining whether the disease is hereditary. Identifying a germline RB1 mutation has implications for treatment planning, long-term surveillance, and genetic counseling for family members. (1), (2), (3)

Endophytic growth describes the process where a retinal tumor extends inward through the cavity of vitreous (fig.10). These malignancies penetrate the retina's internal limiting membrane, leading to vitreous seeding, which is the spread of living tumor fragments within the vitreous. In clinical context, this manifests as vitreous haze and suspended opacities visible during examination. (1), (3)

Exophytic growth arises when a tumor develops outward into the subretinal space. These exophytic retinoblastomas frequently induce severe exudative retinal detachments, which could mask the tumor and lead to subretinal seeding. Mixed growth pattern, combining both endophytic and exophytic features is exhibited in larger tumors (fig.11). (1), (3)

Diffuse infiltrating retinoblastoma, the least common pattern, lacks a distinct mass and instead causes diffuse retinal thickening without classic calcifications. It may present with chemosis, pseudohypopyon (fig.12), or pseudovitritis, making diagnosis challenging. (3)

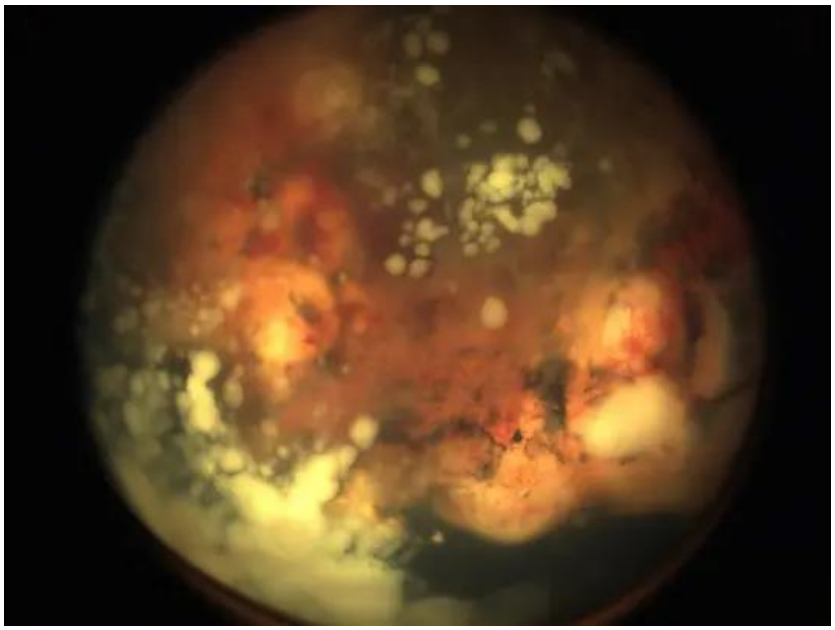

Fig.10 Endophytic growth pattern in retinoblastoma (3)

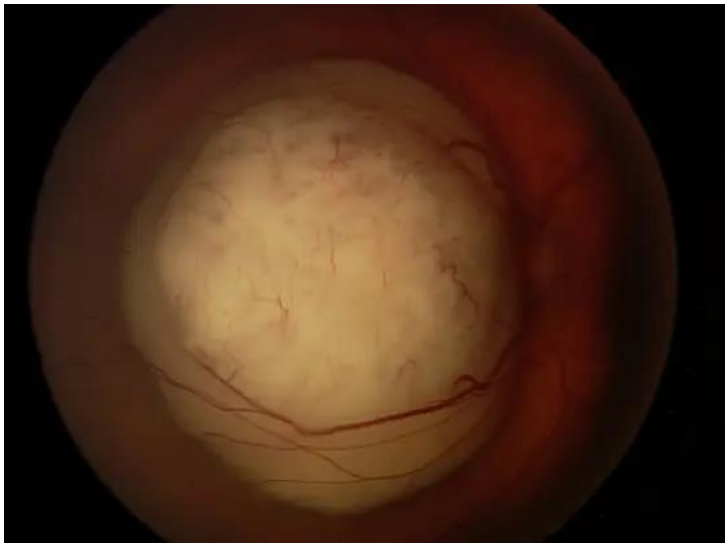

Fig. 11 Mixed endophytic and exophytic growth pattern in retinoblastoma (3)

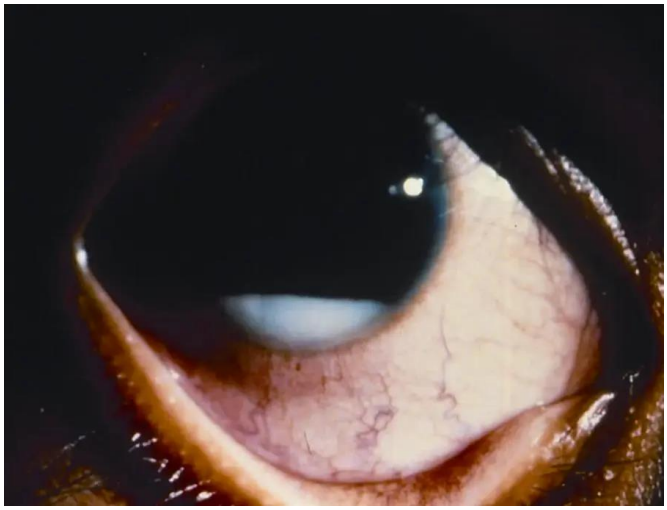

Fig. 12 Appearance of pseudohypopyon associated diffuse infiltrating retinoblastoma. (3)

While these patterns are primarily identified during funduscopic examinations, further evaluations should involve axial (A) and brightness (B)- scan ultrasound, which is beneficial for diagnosis and describing retinoblastoma. A-scan provides precise measurement of tumor dimensions and internal reflectivity, while B-scan generates cross-sectional images of the eye. On B-scan ultrasound, the existence of a hyperechoic, dome-shaped mass with intralesional calcifications and posterior acoustic shadowing (Fig.13) is strongly indicative of retinoblastoma in pediatric patients. This imaging technique also provides information about the tumor's size, as well as confirming any retinal detachment. (1), (3)

While computerized tomography (CT) scans can effectively reveal calcium deposits and

provide information about tumor size in retinoblastoma cases, they are generally not recommended. Instead, magnetic resonance imaging (MRI) is preferred when available. This preference stems from the fact that CT scans expose patients, especially those germline mutations, to radiation. Such exposure can increase the chance of developing secondary malignancies in those susceptible individuals. Therefore, to minimize potential long-term risks, MRI is considered the safer and more appropriate imaging modality for evaluating retinoblastoma. MRI is useful in assessing extraocular extension, optic nerve involvement (Fig.14), along with identifying associated primitive neuroectodermal tumors (PNET), as in cases of trilateral retinoblastoma with pinealoblastoma (Fig.15). In cases where there is concern about the extent of retinoblastoma, in particularly when extraocular spread is suspected. Addition diagnostic procedures include bone marrow examination and lumbar puncture to rule out the presence of cerebrospinal fluid (CSF) or bone marrow metastases. (1),(3), (17)

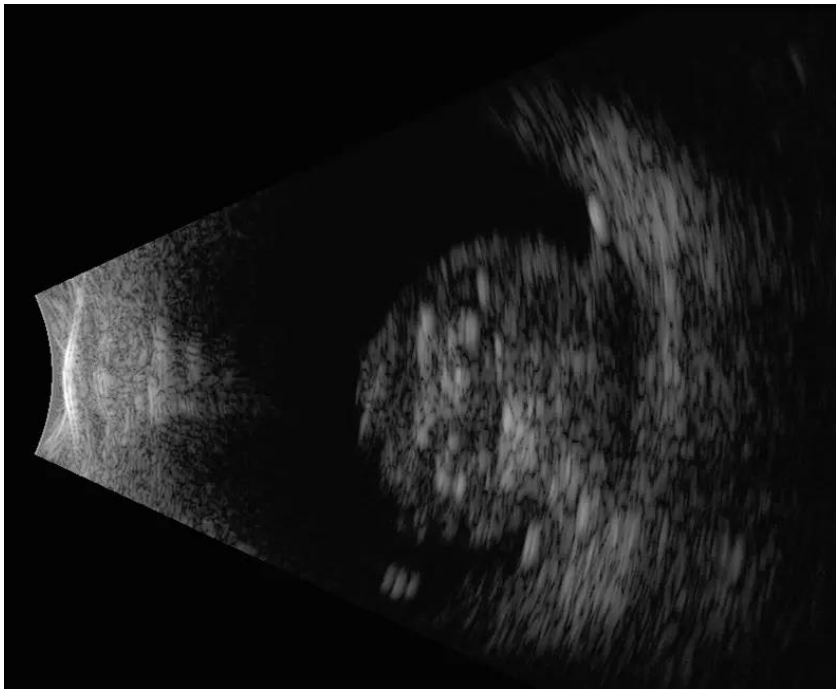

Figure 13. Retinoblastoma as visualized by B-scan ultrasound reveals a dome-shaped mass originating from the retina with intralesional calcification. (3)

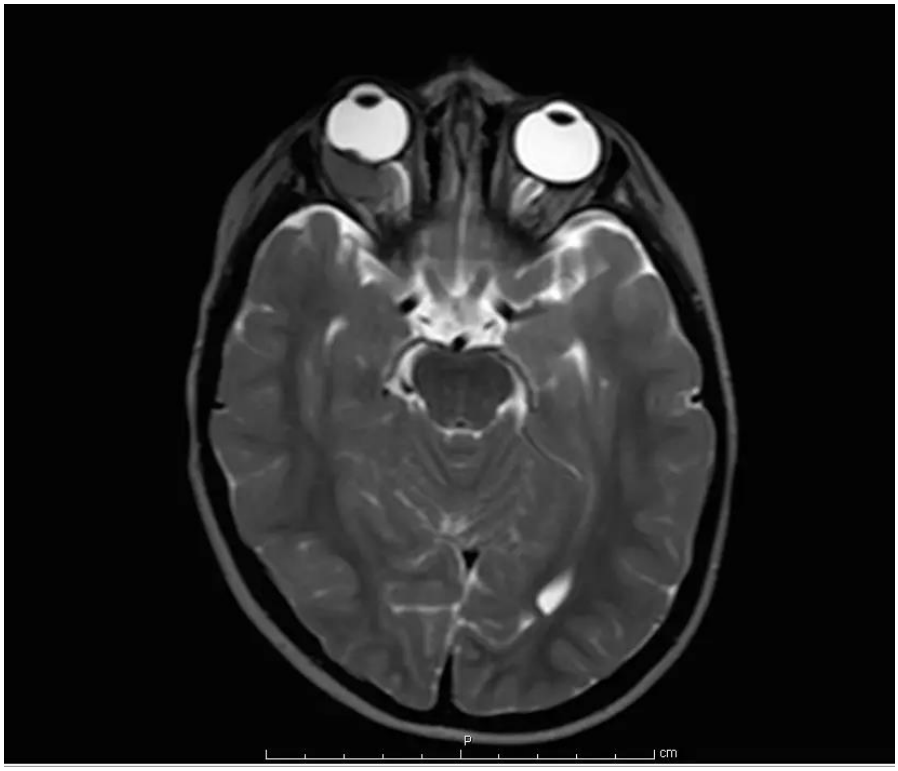

Fig. 14 Magnetic resonance imaging (MRI) scan revealing a right-sided intraconal orbital mass that is hypointense compared to the vitreous. (3)

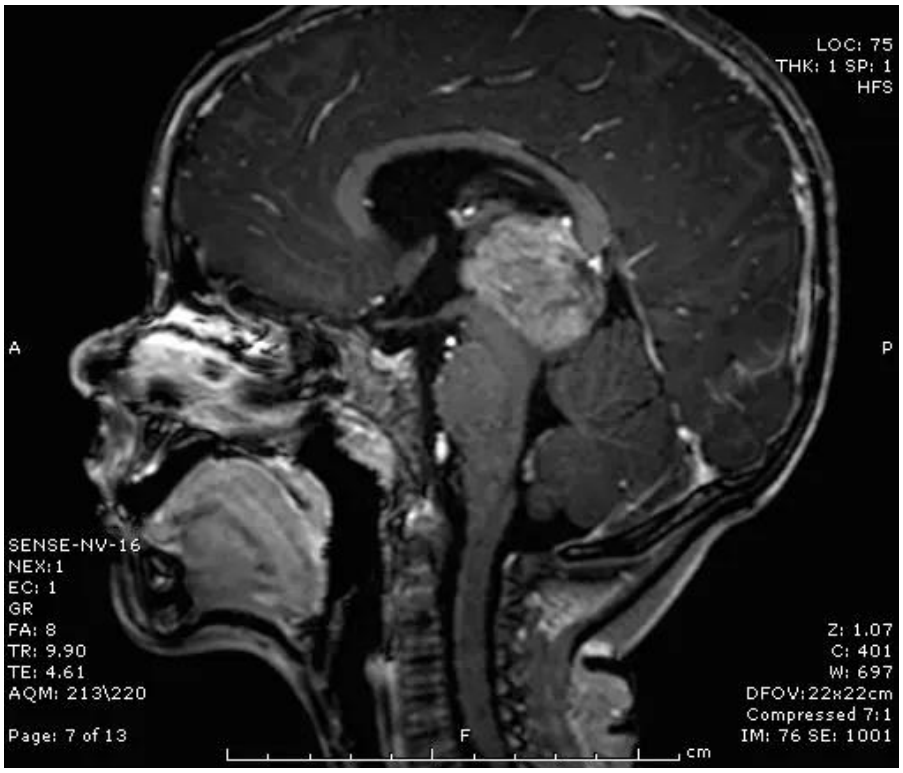

Fig. 15 MRI revealing an irregular, indistinct mass consistent with a primitive neuroectodermal tumor (PNET) in a child with bilateral retinoblastoma (3)

4.9 Differential diagnosis

The diagnostic consideration for retinoblastoma consists of several conditions which can be accompanied by overlapping clinical features. While leukocoria is a classic sign of retinoblastoma, it is not exclusive to this disease and can also be seen in others, including Coats' disease, a rare retinal vascular disorder causing abnormal blood vessel leakage and retinal detachment; retinopathy of prematurity, which affects premature infants and leads to abnormal retinal blood vessel development, and persistent fetal vasculature (PFV), a congenital anomaly where fetal eye blood vessels fail to regress. (1), (3)

Additional differential diagnosis includes congenital cataract (an opacity of the lens present at birth); toxocariasis (a parasitic infection causing to retinal inflammation); choroidal coloboma (a congenital defect resulting in a gap in the choroid layer of the eye); and vitreous hemorrhage (bleeding into the eye's vitreous body). Other differentials include myelinated retinal nerve fibers and tumors such as astrocytic hamartoma, benign growths arising from retinal glial cells. (1), (3)

In some cases, a white reflex (leukocoria) may also result from corneal opacities, although these can typically be differentiated through a thorough clinical examination. (1), (3)

Coats' disease is among the most important conditions to consider, as it can closely mimic retinoblastoma. It is non-hereditary retinal vascular disorder that typically presents unilaterally in boys aged 6 to 8 years, which is generally older than the average age of onset for retinoblastoma. Clinically, Coats' disease is characterized by dilated and tortuous retinal vessels, telangiectasia, and massive subretinal exudation that may simulate a yellowish, tumor-like mass. Fluorescein angiography is a valuable tool for differentiation, in Coats' disease the angiogram typically shows focal telangiectasia, significant vascular leakage, and subretinal exudates. In contrast, retinoblastoma usually demonstrates dilated vessels with areas of non-perfusion and less leakage. These vascular patterns are key in distinguishing between the two. (1), (3)

Persistent fetal vasculature (PFV) is a congenital anomaly that typically manifests with leukocoria in early infancy. PFV typically occurs unilateral and is often found along with microphthalmia. Common features include cataract formation, elongated ciliary processes, a retrolental mass, and a shortened anterior-posterior axial length compared to the healthy eye. These findings can be detected using A-scan and B-scan ultrasonography, especially in the absence of calcification, which is a hallmark feature of retinoblastoma. Retinal detachments, whereas retinoblastoma is more commonly associated with exudative detachments, subretinal

fluid and potential tumor seeding. (1), (3)

Ocular toxocariasis can also simulate retinoblastoma, particularly when it presents as a white, elevated peripheral retinal lesion. Unlike retinoblastoma, ocular toxocariasis is typically unilateral and is often accompanied by significant inflammatory signs such as conjunctival injection, ocular pain, photophobia, and inflammatory cells in the anterior chamber or vitreous. This condition tends to present with more pronounced inflammation compared to retinoblastoma. A detailed patient history is essential, as contact with puppies younger than six months, which carry a high prevalence of Toxocara infection, or a history of geophagia (soil ingestion) are common routes of transmission. Systemic signs like fever, eosinophilia, pneumonitis, or hepatosplenomegaly may indicate visceral larva migrans. Diagnosis is further supported by positive serologic testing for Toxocara canis antibodies. (3), (18)

4.10 Staging and Classifications of Retinoblastoma

Retinoblastoma can be staged using several detailed systems. For clinical decision-making, tumors are broadly categorized as intraocular or extraocular. (3), (13)

Extraocular cancers are further classified to orbital retinoblastoma, involving solely the eye socket, while metastatic retinoblastoma indicate dissemination to distant sites for instance the brain or bone marrow. (3), (13)

There are two main classifications systems used for intraocular retinoblastoma. The Reese-Ellsworth system, involved in the 1950s, remains a foundational tool which assesses the likelihood of preserving the eye after radiation therapy by categorizing patients into five prognostic groups (3):

- Group I (Very favorable):

  Solitary tumors smaller than 4 disc diameters (DD) located at or behind the equator, or multiple tumors none exceeding 4 DD in size, all situated behind the equator.

- Group II (Favorable):

  Solitary tumors measuring 4-10 DD at or behind the equator, or multiple tumors 4-10 DD in size behind the equator.

- Group III (Doubtful):

  Any tumor anterior to the equator, or solitary tumors larger than 10 DD behind the

equator.

- Group IV (Unfavorable):

  Multiple tumors with some exceeding 10 DD, or any lesion extending anteriorly to the ora serrata.

- Group V (Very Unfavorable):

  Massive tumors involving over half the retina or cases with vitreous seeding. (3)

As treatment options advanced, physicians increasingly favored chemotherapy over external beam radiation due to evidence showing increased risk of secondary tumors developing after radiotherapy. The Reese-Ellsworth system became less relevant for predicting outcomes with modern therapies. As result, the Internation Classification of Intraocular Retinoblastoma (ICRB) was created to more reliably identify which patients with intraocular retinoblastoma could be cured and while preserving the eye and avoid removal of the eye (enucleation) or external beam radiation. The ICRB system categorize tumors into groups A through E based on the following characteristics and is illustrated visually in Fig.16, (3), (15):

- Group A: Small tumors (3 mm or less across) that are only in the retina and are located >3 mm from the foveola and > 1.5 mm from the disc.
- Group B: Tumors larger than 3 mm or in a macular or juxtapupillary location, potentially with a cuff of subretinal fluid < 3 mm from the tumor without associated subretinal seeding.
- Group C: Tumors with localized subretinal or vitreous seeding (Figure 8) within 3 mm of the tumor and up to 1 quadrant if subretinal fluid.
- Group D: Tumors with diffuse subretinal or vitreous seeding > 3 mm from tumor and extensive subretinal fluid.
- Group E: Extensive retinoblastoma with poor prognostic signs, including neovascular glaucoma, tumor anterior to the vitreous face (figure 8), diffuse infiltrating retinoblastoma, phthisis bulbi, aseptic orbital cellulitis, or opaque media from diffuse vitreous hemorrhage (Fig.17, right).

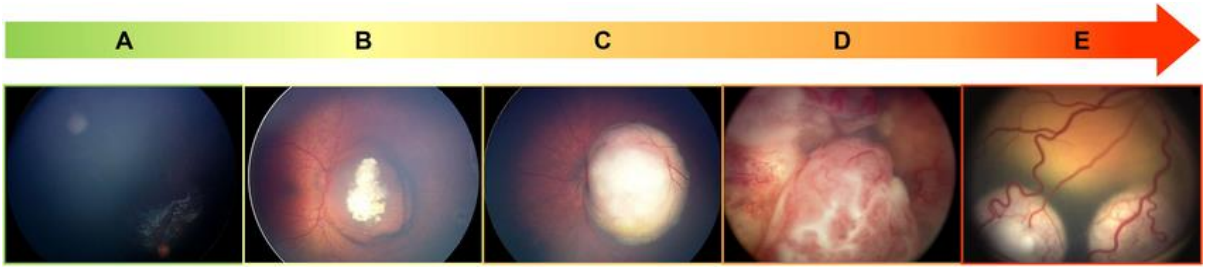

Fig. 16 The graphic illustrates the International Classification of Retinoblastoma (ICRB), categorizing the disease into groups A through E based on five different patients presenting at various stages. (15)

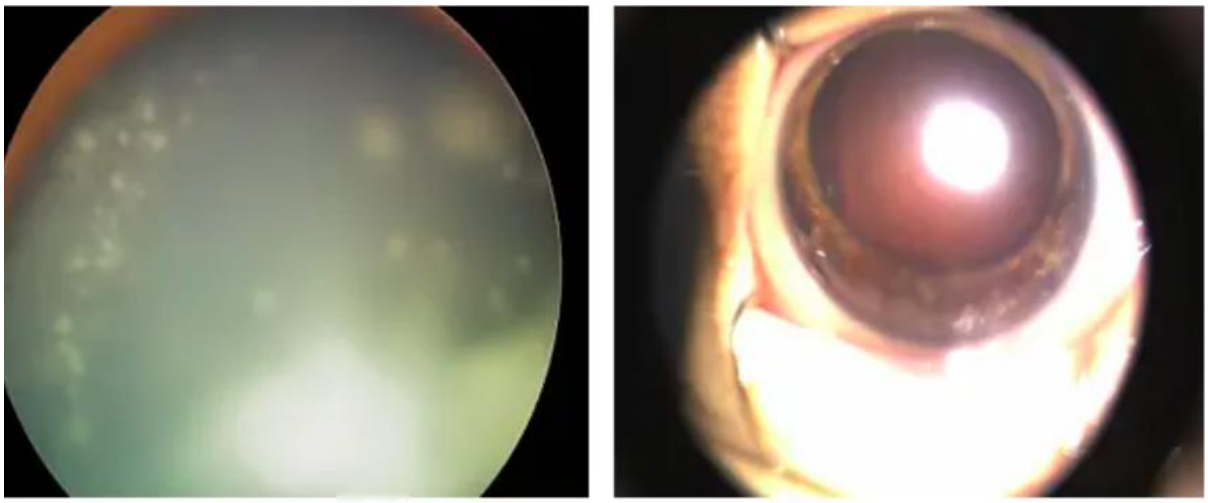

Fig. 17 Left: Presence of vitreous seeding. **Right**: Involvement of the anterior segment characterized by nodular opacities on the iris and diffuse vitreous hemorrhage. (3)

Based on the extensive patient data, the ICRB classification has proven reliable tool in predicting the success of the eye preservation during the chemoreduction era. Group D eyes treated with IV chemotherapy have shown positive results. (3) In a study involving 62 Group D eyes, systemic chemoreduction successfully preserved 47% of these eyes without additional interventions. (13) For cases with tumor recurrence, intensity-modulated radiation therapy (IMRT) was used as a salvage treatment, achieving globe salvage in 79% of the irradiated eyes. (13) Overall, Kaplan-Meier analysis, a statistical method that calculates cumulative survival rates over time while adjusting for censored data, such as patients who were lost to follow-up. The analysis showed that globe survival rates for Group D eyes were 82% at 12 months and 68% at 60 months, highlighting the effectiveness of combined treatment approaches in preserving vison and functionality in many cases. (13)

However, Group E eyes have substantially reduced likelihood of successful outcomes due to the advanced nature of the disease. These cases often necessitate enucleation as the primary

treatment, underscoring the challenges in managing this group with chemreduction alone. (3) (14)

5. Treatment approaches

5.1 Chemoreduction and Consolidation therapy in retinoblastoma

Recent advances in chemotherapy have significantly improved the management of retinoblastoma. The main goals of current treatment are to preserve the patient's life, preserve the eye as an organ, and maintain as much visual function as possible. (2)

In non- heritable, unilateral cases, enucleation, the surgical removal of the affected eye is often enough to cure the disease. Success rates in these cases range from 65% to 95%. However, if tissue analysis shows elevated risk features such as deep invasion into the choroid or inlovement of the optic nerve, further treatment using chemotherapy is usually recommended. Common chemotherapy combinations include DC (vincristine, doxrubicin or idarubicin, and cyclophosmaide), VCE (vincristine, carboplatin, etoposide). (2)

For initial-stage unilateral condition, particularly in children in younger age who might later develop bilateral involvement, a more conservative, eye-sparing approach is advised. (2)

In bilateral or heritable cases, systemic chemoreduction is typically the initial step. This approach uses chemotherapy is given to shrink the tumor before applying more target therapies and involves a combination of vincristine, carboplatin, and etoposide. A two-drug regimen using vincristine and carboplatin has proven effective for Group B tumors, while more advanced tumors such as Group C or D, which may contain vitreous seeds, usually require a three-drug regimen to achieve adequate tumor control. (2)

After initial chemotherapy, consolidation therapy is used to further destroy any remaining tumor tissue. It may be used alone for Group A tumors. The selection of the technique relies on the tumor's position and size. For small tumors located in the front part of the eye, cryotherapy, which involves freezing the tissue, is often applied. Tumors situated in the back of the eye are more commonly treated with laser photocoagulation or thermotherapy, both of which use heat to destroy tumor cells. For larger or treatment resistant tumors, brachytherapy may be considered. This method delivers localized radiation by placing a radioactive plaque directly on the outer surface of the eye. (2)

However, not all tumors respond equally well. Some treatment failures occur because

chemotherapy drugs cannot reach all parts of the tumor, epically if there are tumor seeds in the vitreous or under the retina. Other failures happen because some cancer cells divide slowly or not at all, making them less affected by drugs that target actively dividing cells. (2)

Retinoblastoma can occasionally spread beyond the eye. In cases of recurrence or metastasis, 60% to 70% present with disease limited to the orbit (eye socket). These are treated with combination of chemotherapy and radiation, followed by enucleation and orbital radiation. If cancer cells are located at the end of the removed optic nerve, additional therapy is given, if the lymph nodes near the ear or neck are involved, they may also need to be treated with radiation. (2)

In more severe cases where the disease spreads to the central nervous system (CNS) or other parts of the body, treatment becomes more aggressive. It often includes platinum-based chemotherapy, radiation to the brain and spinal cord, and sometimes large dose chemotherapy followed by a stem cell transplant to support recovery. (2)

5.2 Intra-arterial Chemotherapy (IAC)

Intra-arterial-chemotherapy (IAC) was pioneered in Japan by Dr. Kaneko, an ophthalmologist, as a treatment aimed at preserving the eye in patients with retinoblastoma that had vitreous seeds. Dr. David Abramson, a prominent American ocular oncologist, was the first to utilize the IAC in the United States. Advanced retinoblastomas are treated mainly by IAC, specifically Group D and E cases. The procedure consists of inserting a ballon catheter through the femoral artery and navigating under fluoroscopic into the origin of the ophthalmic artery. When the catheter is securely positioned, a combination of chemotherapy drugs, typically melphalan, topotecan, and/or carboplatin (fig. 24), which is directly infused into the tumor's blood supply. This procedure typically requires several multiple sessions over the duration of weeks to months. According to neuroradiologist, Dr. Pierre Gobin's findings, the two-year ocular event free survival rate is around 70% for all eyes, 80% for eyes that has never received intervention and 60% for eyes with previous unsuccessful treatment. (2) Despite this, there are risks and limitations including potential complications such as eyelid erythema/edema (redness and swelling), emboli to the retina/choroid with occlusive vasculopathy (blockage of small blood vessels in the eye leading to tissue damage), vitreous hemorrhage (bleeding into the eye's vitreous body) and cerebral vasoconstriction (narrowing or clotting of the main artery supplying the eye). There is an ongoing debate regarding that systemic chemoreduction is protective against retinoblastoma metastases and/or third tumor (pinealblastoma) whereas localized IAC does not provide this protection. Addition debate

concerns the possibility that IAC might mask histologic high-risk factors in eyes with extensive retinoblastoma which later undergo enucleation. The viable treatment option for patient is IAC. (2), (20)

5.3 Intravitreal injections

Despite long-standing cautions against intraocular needle procedures in pediatric retinoblastoma cases due to tumor seeding risks, researchers have explored intravitreal chemotherapy injections since the early 1960s. This approach challenged the traditional advice given to Opthalmic surgeons, who were previously were cautioned against passing needles through the eye wall into the vitreous of children with retinoblastoma. Both ophthalmologists, Dr. Ghassemi and Dr. Sheilds, explored the use of intravitreal melphalan both alone and in combination with topotecan, as a treatment strategy for vitreous seeds in retinoblastoma cases. This method involves directly injecting chemotherapeutic agents into the vitreous cavity to target persistent or recurrent tumor seeds (Fig.18). (2), (20)

Dr. Munier, a Swiss ophthalmologist describes a method for treating persistent or recurring retinoblastoma vitreous seeds using intravitreal melphalan injections. This technique involves utilizing a 32-gauge needle attached to a tuberculin syringe, which is carefully positioned at the pars plana (Fig.19), and applying cryotherapy to the needle as it exits the eye, aiming to prevent tumor cells from spreading along the injection path. The injection is performed by advancing the needle into the vitreous and delivering the drug (Fig.20). The procedure incorporates safety measures to lower the risk of extraocular tumor spread while delivering targeted chemotherapy to the vitreous cavity. In this technique, it was noted that there was no tumor seeding in 135 total cases. Intravitreal injection was successfully administered in 237 eyes from 227 patients, indicating that some patients had retinoblastoma in both eyes. Only one case of extra-ocular tumor spread was reported, making this highly effective treatment option. A follow up case demonstrated complete regression of vitreous sees and no signs a of extraocular extension after weekly topotecan injections (Fig.21). Innovative injection methods for local administration of chemotherapeutic agents against retinoblastoma are under development and as these techniques are refined, they are expected to gain wider use. (2)

Advancements in targeted treatment of retinoblastoma have progressed in tandem with developments in intravitreal injections. These advancements encompass gene therapy and nanotechnology, paving the way for innovative treatment approaches. A study explored the use of intravitreal injections of an adenovirus vector containing the herpes simplex thymidine kinase gene in patients with bilateral retinoblastoma and vitreous seeds. This treatment,

combined with intravenous ganciclovir, resulted in long-term regression of vitreous seeds in one patient. (2),

Further research focuses on periocular injections of nanoparticles containing carboplatin and intravitreal topotecan in a rabbit model of retinoblastoma. Preliminary results suggest that therapeutic levels of intravitreal topotecan can be achieved, successfully eliminating vitreous seeds in the model. (2)

Furthermore, a new method being explored is the injection of topotecan into the suprachoroidal space using microneedles. This technique potentially allows for targeted drug delivery with minimal risk of extraocular tumor spread, as neither the vitreous nor subretinal spaces are penetrated. (2)

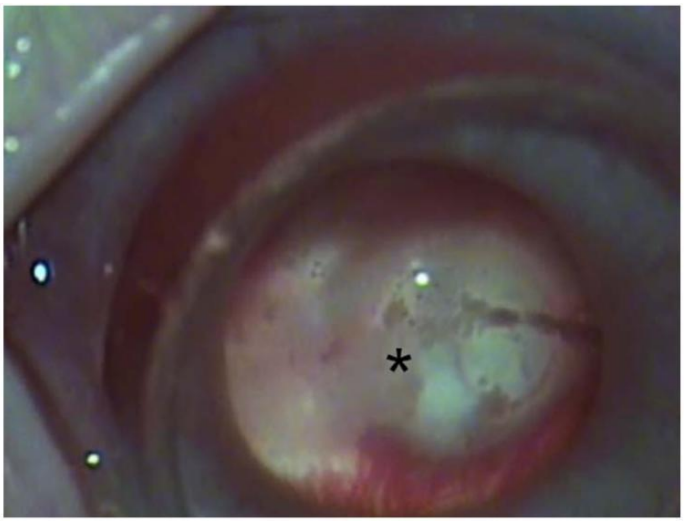

Fig. 18 In the rabbit model, vitreous seeds characteristic of retinoblastoma (*) are noted. (2)

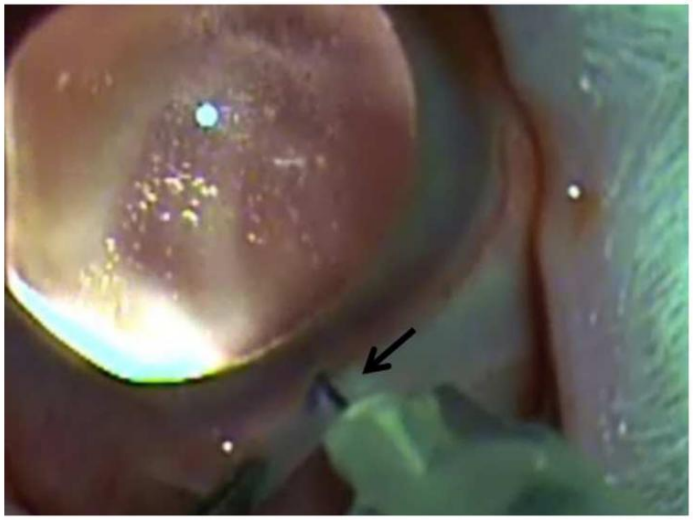

Fig. 19 The arrow indicates 32-gauge, 4 mm needle positioned at the pars plana. (2)

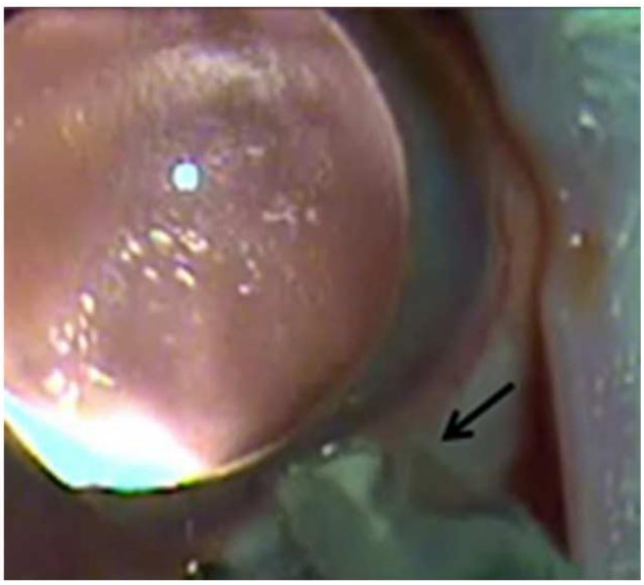

Fig. 20 After advancing the needle (arrow) to its hub, topotecan is injected into the vitreous cavity (2).

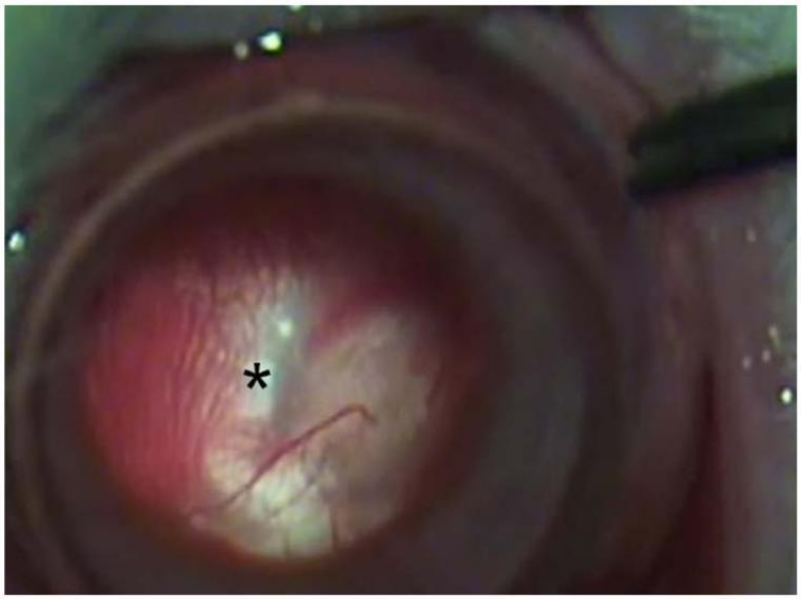

Fig. 21 After receiving 20µg of topotecan weekly over three weeks, the patient shows no remaining vitreous seeds, normal retinal/optic nerve findings, and no spread of extraocular tumor. (2)

5.4 Prognosis and follow up

Children receiving eye-preserving therapies (external beam radiation, chemoreduction) require regular anesthesia-assisted follow-up exams to detect potential recurrence. Each

evaluation should closely track tumor regression, documenting key details like appearance, size, location and tumor count. Post treatment, regressed tumors may present as calcified white masses, translucent, fish flesh-like tissue. A standard monitoring schedule involves general anesthesia exams every 4-8 weeks until age 3. If the disease stabilizes, fewer exams are needed. However, retinoblastoma recurrence, even years later, is common in treated lesions. (3)

Patients with hereditary retinoblastoma require lifelong systemic oncology monitoring due to their elevated risk of secondary malignancies. The most frequent secondary cancer is osteosarcoma, though other tumors, such as primitive neuroectodermal tumors (PNETs), fibrosarcoma, and melanoma may also develop. Radiation therapy further increases this risk, especially within the treated area. Long-term ophthalmic and oncologic surveillance is essential for all retinoblastoma survivors, with special vigilance for those carrying germline mutations. (3)

6. Clinical Case: Diagnosis Retinoblastoma unifocal gr. B OS

A premature female infant, born on September 24, 2015, and the firstborn of twins delivered by Caesarean section at 35 weeks of gestation. The birth weight was 2600 grams, and the Apgar score was 10/10. (21)

At 7 months of age, an intraocular tumor was first detected on May 12, 2016, during a routine ophthalmological examination. The patient was examined at the Eye department of Vilnius University Children's Hospital. (21)

The right eye: Normal (21)

The left eye: A single tumor approximately 3 PD size was identified in the central retina covering an upper half of the optical nerve disc. Fundus photography captured the lesion near the optic disc (Fig.22 and Fig.23). (21)

Ultrasonography showed dome-shaped lesion with moderately high internal acoustic reflectivity throughout in the left eye. (21)

MRI imaging on May 31, 205, revealed a large compact tumor in the optic nerve area 3,6x2 mm size (Fig.24, Fig.25). (21)

Following treatment, fundus photography demonstrated an elevated mass disrupting the normal retinal structure, consistent with residual retinoblastoma lesion (Fig. 25). (21)

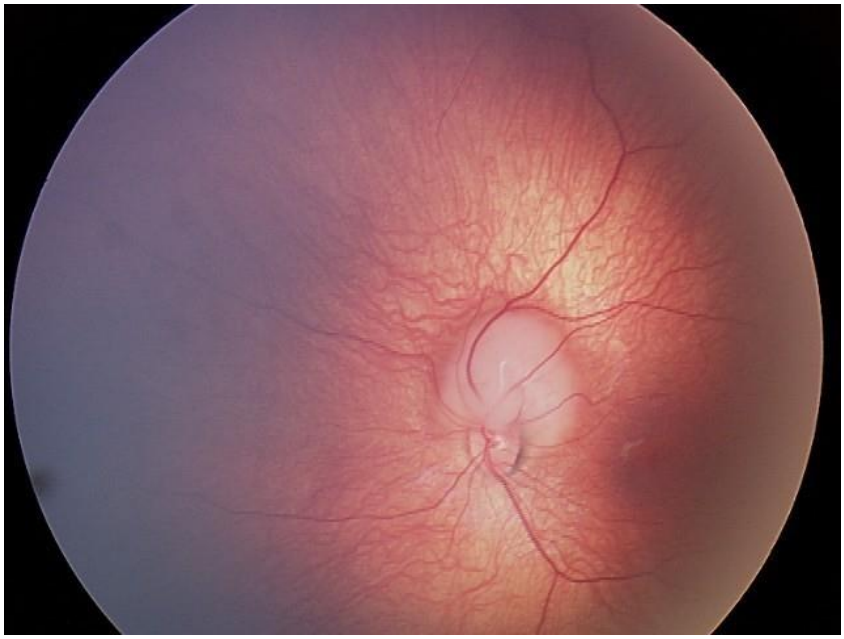

Fig. 22 Fundus photograph of the left eye at initial detection. It captures the back of the eye, including the retina, optic disc and blood vessels. In the image shows a tumor located in the retina, near the optic disc. Image courtesy of Dr. Aušrinė Misevičė, unpublished case study 2025. (21)

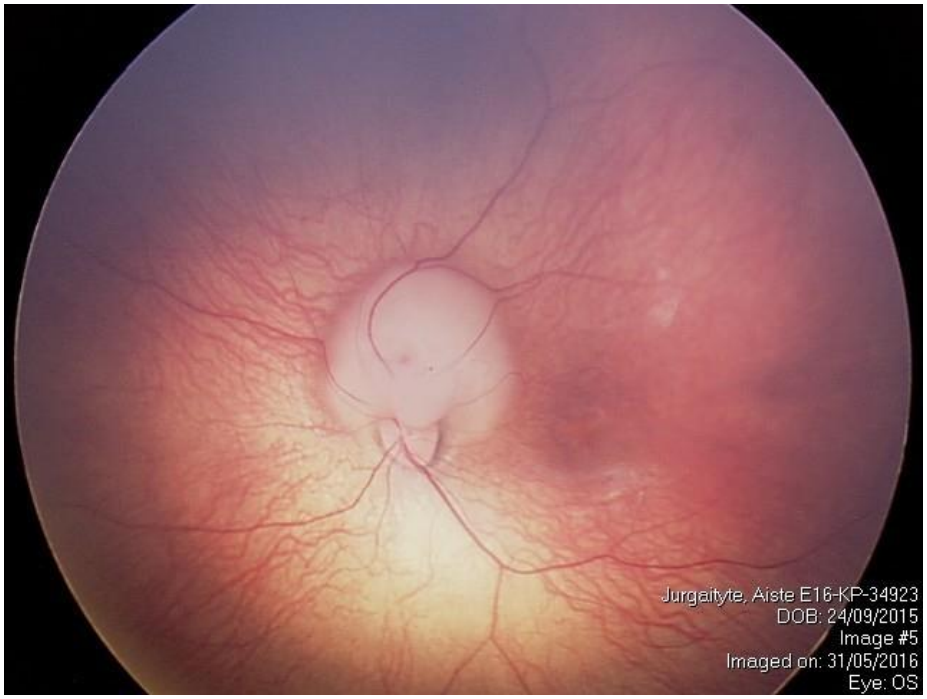

Fig. 23 A fundus photograph of the left eye with a tumor near the optic disc. (21)

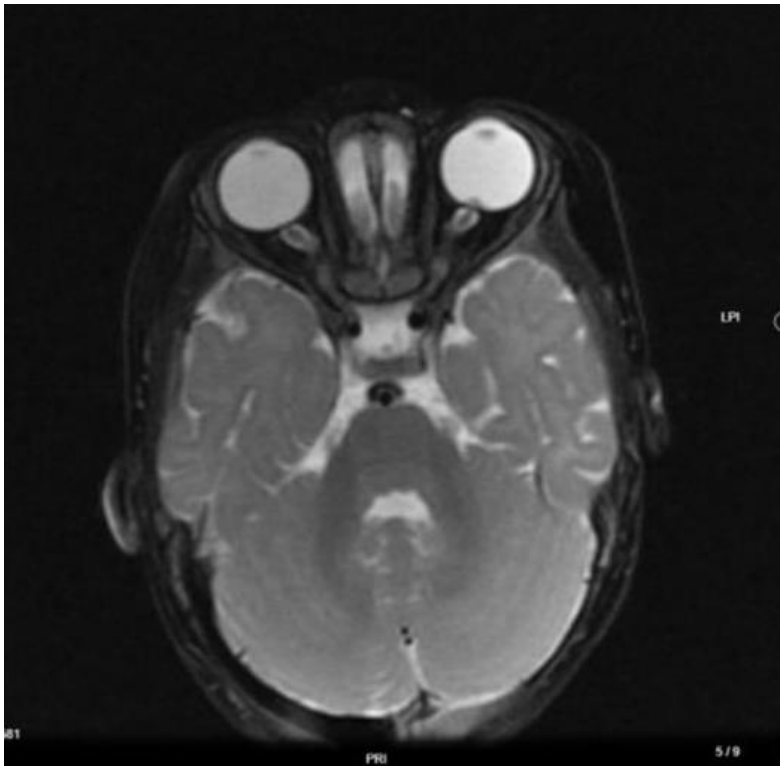

Fig. 24 Axial MRI demonstrating the tumor in the optic nerve region. (21)

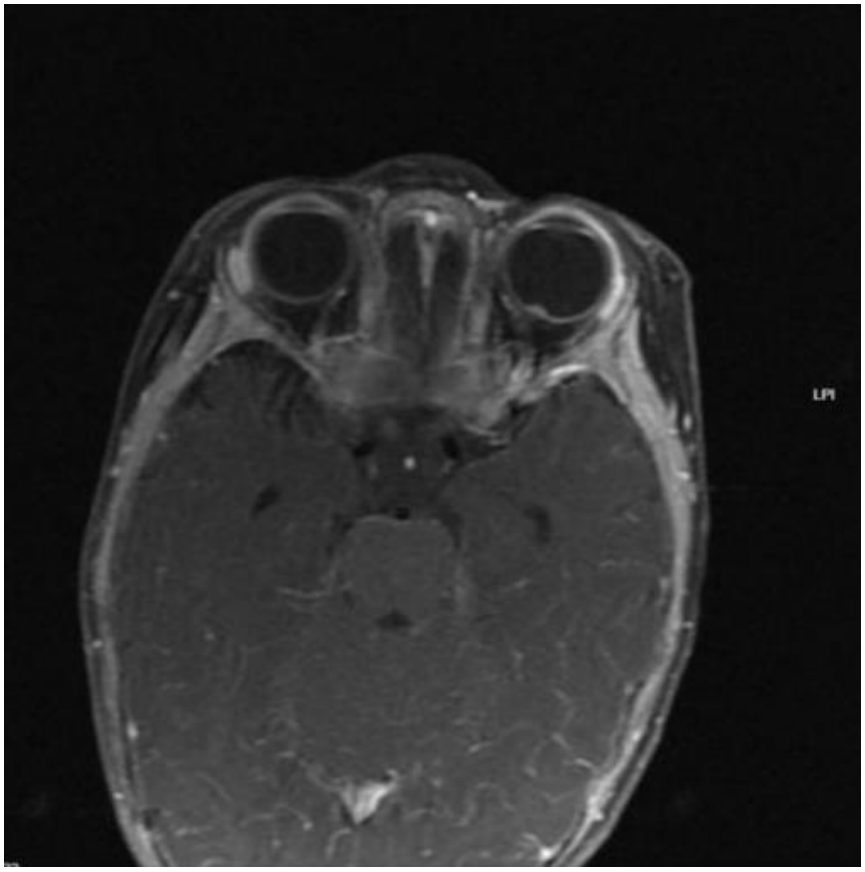

Fig. 25 Axial MRI demonstrating the tumor in the optic nerve region. (21)

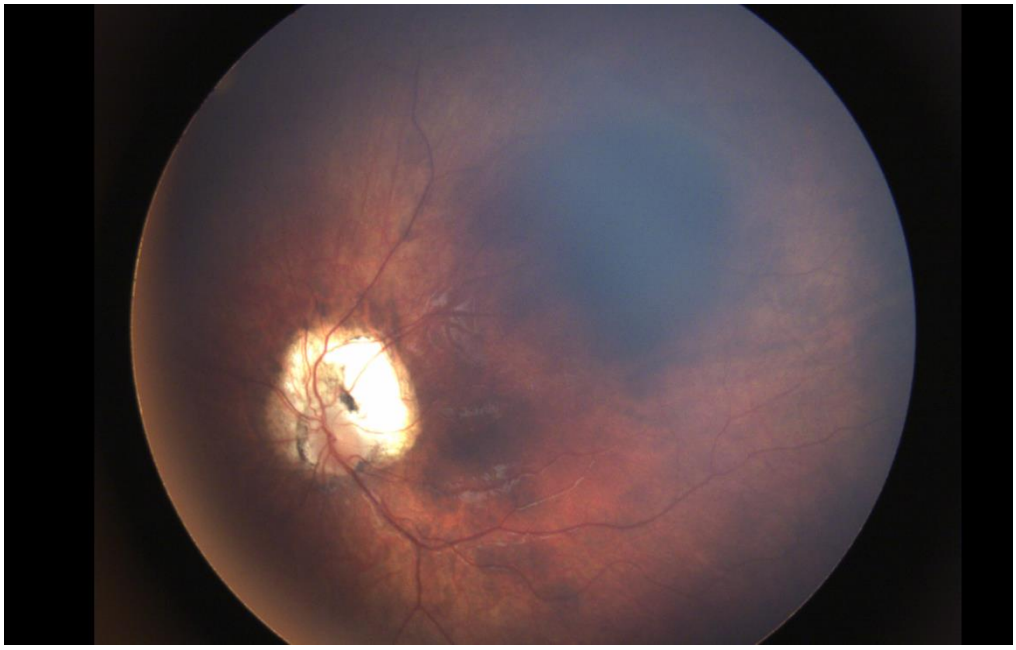

Fig.26 Fundus photography after the treatment reveals an elevated mass disrupting the normal retinal layers, consistent with a retinoblastoma tumor. (21)
The patient was consulted by colleagues in Switzerland, who agreed to take over the treatment. (21)

The patient was treated in Lausanne, Switzerland, starting on June 10, 2016. The treatment consisted of:

- 2 intra-arterial Melphalan injections (2016-06-22 and 2016-07-16);
- 1 combined intra-arterial Melphalan/Topotecan injection (2016-08-17);
- OS thermotherapy (2016-06-10, 2016-08-09, 2016-10-31 and 2016-11-17); (21)

The last examination and treatment were on May 22, 2017. Further examinations under general anesthesia and treatment according to the results every 4 weeks were recommended in Jules Gonin Eye Hospital and CHUV (Centre Hospitalier Universitaire Vaudois). A follow up appointment was booked for July 6, 2017. The patient was treated in Switzerland once more in 2017 with one additional intra-arterial chemotherapy session. In total she received four intra-arterial chemotherapy sessions and four transpupillary thermotherapy sessions. (21)

After the treatment, regular check-ups were conducted every six months in Lithuania. Amblyopia prevention treatment – occlusion therapy was continued until 2024. In 2024, the patient stopped patching the healthy eye, and the visual acuity on March 13, 2024, of the left eye decreased to 0.4 for distance and 0.5 for near vision. (21)

The last check- up were on March 12, 2025. Visual acuity (21:

OD = 1,0
OS = 1,0 (-2) (letters)

From the near V

OD = 1,0

OS = 1,0

6.1 Analysis of Case Study and Treatment

The clinical case of a premature infant diagnosed with unifocal Group B retinoblastoma in the left eye (OS) presents a compelling opportunity to analyze the diagnostic approaches, the treatment strategies, and genetic considerations that define current retinoblastoma management.

The detection of the intraocular tumor during a routine ophthalmological examination, despite the absence of typical presenting signs such as leukocoria or strabismus, underscores the importance of vigilant screening, particularly in infants with risk factors like prematurity. The absence of the typical presenting signs in this case emphasizes that reliance solely on these key indicators can lead to delayed diagnosis. Routine screening, as portrayed in this case, facilitates early detection, a factor significantly impacting general prognosis.

The classification of the tumor as "unifocal, Group B" is crucial for determining the appropriate treatment strategy and predicting visual outcomes. According to the Reese-Ellsworth classification, Group B tumors indicate a relatively limited extent of disease within the retina. This categorization suggests a higher likelihood of successful globe salvage with vision preservation comparted to more advanced groups. The use of ultrasonography and MRI to confirm the diagnosis and assess tumor size and location aligns with established diagnostic protocols. These imaging modalities provide complementary information about the tumor's characteristics and potential extraocular extension. The MRI finding of a 3.6 x mm tumor in the optic nerve area is of particular importance, as optic nerve involvement can influence treatment decisions and prognosis. This is further illustrated in the #D disc topography (Fig.27), where the left optic nerve (OS) shows structural abnormalities likely related to the tumor and prior treatment.

The patient's treatment regimen in Switzerland, consisting of intra-arterial chemotherapy (IAC) with melphalan and topotecan, combined with transpupillary thermotherapy (TTT), reflects a contemporary, multimodal approach to localized retinoblastoma, offering the advantage of delivering high concentrations of chemotherapeutic agents directly to the tumor

while minimizing systemic toxicity. This approach is particularly beneficial in young children, where minimizing systemic exposure is crucial to reduce the risk of long-term side effect.

The goal of this strategy was to preserve the affected eye and its function while achieving effective tumor control. The treatment appears to have been successful, with no reported tumor progression or recurrence since the last intervention in 2017. Ongoing monitoring has been ensured through regular follow-ups every six months in Lithuania. Follow-up imaging, including a fundus photograph and OCT scan (Fig.28), confirms the anatomical differences between the healthy right eye (OD) and the treated left eye (OS), where residual retinal changes from the tumor and treatment are evident.

A significant challenge throughout the management of this case has been addressing amblyopia in the affected left eye. Although the patient initially followed occlusion therapy, they discontinued patching the healthy eye in 2024 leading to a decline in visual acuity in the left eye. The patient resumed patching therapy and continued it consistently until 2025. By March 2025, visual acuity had recovered to average vison, demonstrating the critical role of sustained adherence to amblyopia treatment.

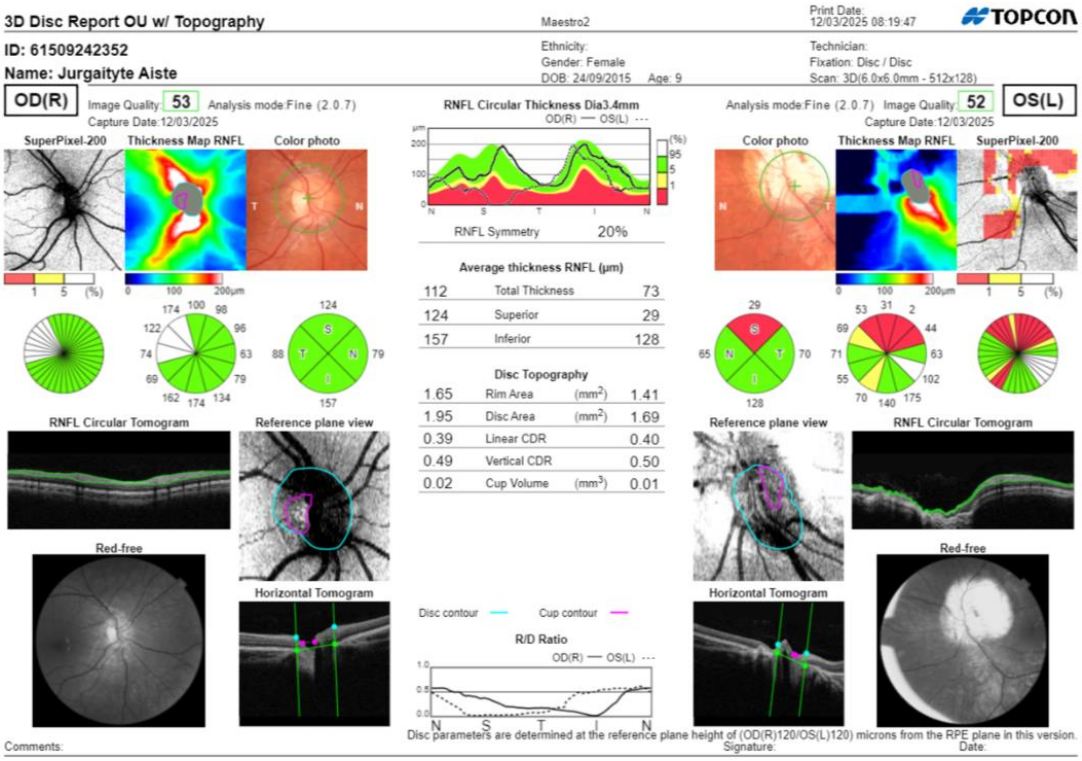

Fig.27 3D disc report OU with Topography. The right optic nerve (OD) exhibits normal structures and thickness. The left optic nerve (OS) shows abnormalities, potentially due to the

tumor’s impact and/or previous treatment. (21)

Fig. 28 Fundus photograph and OCT scan showing both the right (OD) and left (OS) eye. The right eye exhibits normal anatomy. The left eye shows a large tumor mass in the retina, which is confirmed by the OCT image disrupting the normal retinal structure. (21)

7. Summary of results and future research

This thesis has explored the clinical and genetic aspects of retinoblastoma, emphasizing the critical role of early detection and access to advanced treatment modalities in determining patient outcomes. The findings highlighting the importance of genetic testing for RB1 mutations, which is essential for early diagnosis and risk stratification, enabling timely preventive interventions for individuals with hereditary predisposition. Modern therapeutic strategies, particularly intraarterial chemotherapy, have demonstrated encouraging results with high rates of ocular preservation in advanced-stage cases. However, significant disparities in survival rates persist globally due to lack of knowledge and limited access to relevant medical equipment. Intravitreal injection of melphalan is currently used as an effective treatment for vitreous seeding in retinoblastoma, with increasing clinical adoption worldwide.

Future research should focus on developing affordable diagnostic tools to improve early detection in low-resource areas. There is also a need to explore target therapies for aggressive subtypes, particularly those driven by MYCN amplification as these types are a lot more

resilient. Long-term studies are essential to better understand the risks of secondary malignancies in patients with germline mutations. While advancements in drug delivery systems could minimize systemic toxicity and enhance treatment efficacy.

8. Conclusion and recommendations

The clinical case discussed in this thesis illustrates how timely and targeted interventions can help achieve the main goal: saving life, preserving the eye as an organ and protecting vision. However, persistent challenges underscore the need for systemic improvements, particularly in reducing diagnostic delays in low-resource settings, expanding access to specialized care, and ensuring long-term monitoring for high-risk patients, as well as genetic counseling, testing and early detection.

Addressing these gaps requires coordinated global effort. Priorities include implementing standardized newborn eye screening programs to facilitate early diagnosis, establishing regional referral centers with telemedicine and developing standardized protocols for genetic testing and follow up care. Only through such collaborative efforts can we ensure equitable access to life and vision saving interventions for all children affected by this disease.

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