Chirurgia (2025) 120: 294-302
No. 3, May - June

http://dx.doi.org/10.21614/chirurgia.3109

Prevalence and Management of Retinoblastoma. A 10-year Retrospective Analysis from North-Eastern Romania

Vlad Constantin Donica[1,2], Claudia Florida Costea[1]*, Călina Anda Sandu[1,2], Irina Andreea Pavel[1,2] and Camelia Margareta Bogdănici[1,2]

[1]Department of Ophthalmology, Faculty of Medicine, Grigore T. Popa University of Medicine and Pharmacy, Iasi, Romania
[2]Department of Ophthalmology, Sf. Spiridon Emergency County Hospital, Iasi, Romania

***Corresponding author:**
Claudia Florida Costea, MD
Department of Ophthalmology
Faculty of Medicine
Grigore T. Popa University of Medicine and Pharmacy
16 University Street, 700115, Iasi, Romania
E-mail: claudia.costea@umfiasi.ro
ORCID IDs:
Vlad Constantin Donica - 0000-0002-8814-3932
Claudia Florida Costea - 0000-0002-2488-2154
Călina Anda Sandu - 0000-0003-0516-9262
Irina Andreea Pavel - 0000-0002-1116-1585
Camelia Margareta Bogdănici - 0000-0002-9542-7714

Received: 17.01.2025
Accepted: 25.03.2025

Rezumat

Prevalența și managementul retinoblastomului. O analiză retrospectivă pe 10 ani din nord-estul României

Introducere: Retinoblastomul reprezintă cea mai frecventă tumoră oculară pediatrică, iar lipsa testării genetice adecvate şi a înregistrării cazurilor reprezintă unul din principalele motive de prezentare cu tumori în stadii avansate.
Material şi metode: S-a efectuat o analiză retrospectivă între 2014-2024 a pacienților diagnosticați cu retinoblastom în spitalul „Sf. Spiridon", Iaşi, România, urmărind sexul pacienților, vârsta la prezentare, stadiul şi tipul de creştere al retinoblastomului, aspectele histopatologice şi tratamentul efectuat.
Rezultate: Tumorile au fost unilaterale la 9/10 pacienți, iar un pacient a prezentat o formă bilaterală. Vârsta medie a fost de 25,9 luni, cu 7 băieți şi 3 fete. Toți au prezentat tumoră stadiul E. Enucleația a fost realizată în 6/7 cazuri. Doi pacienți au primit tratament conservator, iar un pacient a fost pierdut din urmărire. 42,85% dintre tumori au fost clasificate grad G2, iar 57,15% grad G3. 71,42% au prezentat invazia discului optic, cu afectarea nervului optic în 40% dintre cazuri. Invazia uveală a fost prezentă în 57,14% dintre cazuri.
Concluzie: Rezultatele oferă informații despre opțiunile de tratament şi prognosticul pe termen lung al copiilor cu retinoblastom din nord-estul României. Analiza pe 10 ani a subliniat necesitatea îmbunătățirii măsurilor de screening pentru sugari şi a diagnosticării bolii în stadii precoce.

Cuvinte cheie: retinoblastom, cancer pediatric, calitatea vieții, enucleație

Abstract

Introduction: Retinoblastoma is the most common pediatric ocular tumor and the lack of proper genetic testing and case registration represents an important cause for advanced stage disease at initial presentation.

Material and Methods: A 10-year retrospective analysis of patients diagnosed with retinoblastoma between 2014-2024 in "Sf. Spiridon" Hospital, Iasi, Romania was performed, focusing on patient gender, age at presentation, Rb clinical stage, growth pattern, histological aspects and treatment type.
Results: Unilateral tumors were found in 9/10 patients, one patient having bilateral tumor. Average age was 25.9 months, with 7 male and 3 female patients. All were diagnosed with disease stage E. Enucleation with successful tumor excision was performed in 6/7 cases. Two patients received conservative treatment and one patient was unable to be reached. 42.85% of tumors were classified as grade G2, and 57.15% as G3. 71.42% of cases had optic disc invasion with further nerve invasion in 40%. Uveal invasion was present in 57.14% of cases.
Conclusion: This analysis provides insights into treatment options and long-term prognosis for children with retinoblastoma from the north-eastern part of Romania. This analysis highlights the need to enhance screening measures for infants, because of the advanced stage of retinoblastoma at presentation.

Keywords: retinoblastoma, pediatric cancer, quality of life, enucleation

Introduction

Retinoblastoma (Rb) is the most common malignant ocular tumor found in children, usually under the age of 5. It derives from the primitive neuroectodermal cells, developing in the photoreceptor layers. The initiation is usually performed by a biallelic mutation of the RB1 gene, therefore, requiring two mutations in the same retinal cell precursor. One mutation can develop either at germline or somatic level while the second is usually at the somatic level. The transmission has an autosomal dominant pattern, therefore children born from parents having germline RB1 mutations, have a 50% chance of developing Rb (1-3).

Rb has an incidence of 1:15.000 – 1: 20.000 child births. The highest incidence is re-ported in Asia, followed by Africa, Latin America, North America and Europe, mainly because of natality rate. The Automated Childhood Cancer Information System (ACCIS) analyzed 60 pediatric oncology centers between 1978 and 1997 identifying 1995 cases of Rb from all across Europe. Eastern Europe has the fewest data entries with only Belarus, Estonia, Slovakia and Hungary being among the analyzed countries (4). In a study carried out part of the Surveillance of the Rare Cancers in Europe (RARECARE), Gatta et. al, assessed the incidence, prevalence and survival rate of the main embryonal cancers in Eu-rope, Rb being third in incidence and second in survival rate. They analyzed data from the European Union state members from 1995 to 2002 grouping them according to geographical location. During that time Poland was the only member in the Eastern European group with submitted data (5). In 2021, Stacey et al. performed a report on the European Incidence on Rb and presented incomplete data on several East European countries including Romania, reporting 8 newly found cases in 2017 (6). The lack of proper data gathering highlights the importance of reviewing the current status of patients that were diagnosed with Rb in developing countries.

Histological examinations have shown that Rb cells are undifferentiated having little cytoplasm and intense round basophilic nuclei with granular chromatin and lack of nucleoli (7). The formation of Flexner-Wintersteiner (FW) or Homer Wright (HW) rosettes can be found during hematoxylin-eosin (HE) staining and are characteristic for Rb. They rep-resent a group of cells surrounding a central bundle of neural filaments in HW, while FW rosettes have cells with a center comprised of cytoplasmic tumor cells extension (8).

Based on the stage of the disease, clinical signs can vary from small intraocular tumors with less than 2 mm in size that appear like transparent spots in the retina, to larger tumors with vessels and white calcified lesions before finally reaching a large tumor that can occupy the entire vitreous cavity and touch the lens. All forms can present with leukocoria, from a very subtle aspect, to a completely white pupil in large tumors. While the most common sign found at initial presentation is leukocoria, the second most common is strabismus, and more advanced forms can present with iris colour changes and neovascularization, enlarged cornea and enlarged globe due to increased intraocular pressure and finally proptosis when presentation has been very delayed (9).

Methods

We performed a 10-year retrospective analysis

between 2014-2024 of all electronic medical records of patients that were admitted and diagnosed with Rb in the Sf. Spiridon Emergency Clinical Hospital from Iasi, Romania, that holds the only major child ophthalmology department in the east of Romania. We analyzed patient age, the type of treatment the patient underwent and the results of that treatment, histological and immunohistochemical tumor characteristics, patient quality of life and social reintegration identifying 10 cases of Rb.

This study was performed in accordance with tenets of the Declaration of Helsinki and approved by the Sf. Spiridon Emergency Clinical Hospital ethics committee (Approval no. 65/19.08.2024). Informed consent was obtained from the parents of all subjects involved in the study, during hospitalization. All data were anonymized to ensure patient confidentiality.

Patients suspected for Rb are required to undergo a complete evaluation of the disease in order to establish the best treatment options. Complete blood work and physical examination are usually performed by a pediatric oncologist, while ocular disease evaluation is assessed by an ophthalmologist. A high-resolution magnetic resonance imaging (MRI) of brain and orbits is performed for visualizing the full extent of the disease. In addition, genetic testing and family history are always suggested in order to have a better understanding of the tumor mutation type and to choose a better treatment plan.

Eyes that underwent enucleation had histological examination performed using hematoxylin-eosin (HE) staining protocol and immunohistochemistry (IHC) analysis, highlighting the affinity of neuron-specific enolase (NSE), synaptophysin, S-100 and ki-67 biomarkers for the tumor cells. The American Joint Committee on Cancer (AJCC) classification and the Cancer Staging Manual guidelines classification were used. The analysis was performed during the patient's hospitalization period, with the fragments being sent immediately after surgery. Tumor volume was calculated using V=L*W2/2, where V is tumor volume, L is tumor length and W is tumor width. Patients which benefited from conservative treatment outside of Romania, had their medical history examined during their follow ups.

Results

Two cases had initial presentation in the first year of life, and 8 were diagnosed between 1 and 5 years. Average age was 25.9 months, with a minimum of 4 months and maximum of 5 years. Out of the 10 patients, 9 had unilateral tumors, while 1 patient presented a bilateral case of Rb. Regarding gender, 7 cases were male and 3 were female.

All patients were diagnosed at presentation with clinical stage E (a large tumor touching the lens, with increased intraocular pressure and enlarged globe) (*Fig. 1*). Despite the availability of the medical records, no visual acuity had been recorded due to disease severity and the children's young age at first presentation (*Table 1*).

None of these patients had any prenatal suspicion of intraocular tumors based on the statement of the mothers. Despite our best efforts the parents were unresponsive to performing genetic testing and we possess no data regarding genetic involvement.

One case did not present after initial diagnosis and we were unable to further contact the patient or his legal guardians for treatment and follow-up. The other 9 patients received treatment. 7 patients underwent enucleation with successful tumor excision in oncological safety margins in 6 cases (*Fig. 2*). After surgery, the patients were referred back to the pediatric oncologist for cycles of systemic chemotherapy with Vincristine, Carboplatin and Etoposide according to the national Rb treatment plan.

Histopathological examination of the Rb eyes using HE described a malignant tumor proliferation with dense cellularity formed by small, round or oval tumor cells, with little cytoplasm, hyperpigmented nuclei, intense mitotic activity (*Fig. 3*), both typical and atypical, and large areas of cellular apoptosis with necrosis. In all cases HW

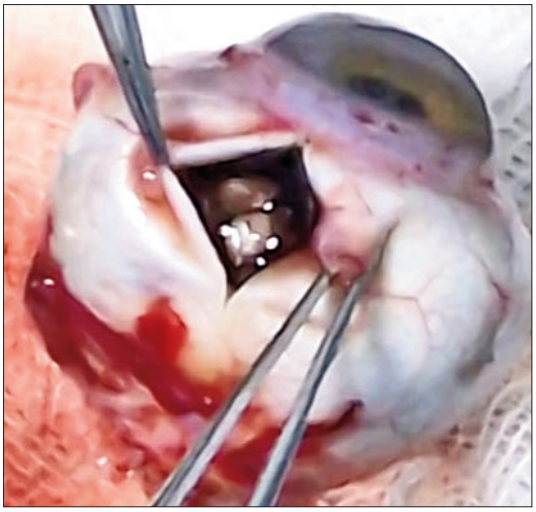

Figure 1. Macroscopic tumor view after eye enucleation

Table 1. Rb prevalence, treatment and follow-up

	Disease stage at diagnosis	Type	Treatment	Follow-up
1	E	Unilateral	Enucleation	No tumor activity, favorable development
2	E	Unilateral	Enucleation	No tumor activity, favorable development
3	E	Unilateral	Enucleation	No tumor activity, favorable development
4	E	Unilateral	Enucleation	No tumor activity, favorable development
5	E	Unilateral	Enucleation	No tumor activity, favorable development
6	E	Unilateral	Enucleation	No tumor activity, favorable development
7	E	Bilateral	Enucleation	Advanced metastatic disease, deceased after 4 months
8	E	Unilateral	Conservative	One cycle of intra-arterial chemotherapy and intravitreal injections, with favorable response
9	E	Unilateral	Conservative	The tumor presents intraretinal and vitreous calcifications and has remain stable with BCVA 20/25,
10	E	Unilateral	Lost	Lost

and FW rosettes could be found, as well as occasional pseudo-rosettes.

Tumor growth pattern was observed to be endophytic in 5 cases, with Rb growing towards the vitreous cavity and exophytic in one case associated with retinal detachment. One case had both exophytic and endophytic growth patterns.

42.85% of tumors were classified (according to AJCC) as grade G2, while the other 57.15% were classified as G3. The optic nerve head was invaded in 71.42% of cases, with continuous invasion of the optic nerve in 40% out of these cases. In one case the tumor had not been able to have a clear resection limit of the optic nerve. Uveal invasion was present in 57.14% of cases.

Based on the histopathological characteristics (according to AJCC Cancer Staging Manual guidelines), 28.57% of cases had L0V0Pn0, 57.14% were L0V0Pn1 and 14,2% were L1V1Pn1 (*Table 2*).

Tumor volume varied from 0.68 cm^3 to 5.66 cm^3, with an average of 3.21 cm^3.

Immunohistochemistry (IHC) was performed in 6/7 enucleated eyes (*Table 3*) and staining showed intense cytoplasmic positivity for synaptophysin and neuron-specific enolase (NSE). The affinity for the S-100 protein was positive in 66.6% cases and inconclusive in 33.3%, while the ki67 biomarker showed in all cases an affinity over 50%.

The patient with unsuccessful tumor excision was the one with bilateral Rb having a delayed initial presentation and diagnosis, and in spite of aggressive intravenous treatment followed by enucleation, the tumor had a recurrence with systemic metastatic disease and the patient did not survive.

The other 6 children had a successful operation with no tumor recurrence and have since received successful ocular prosthesis and if required

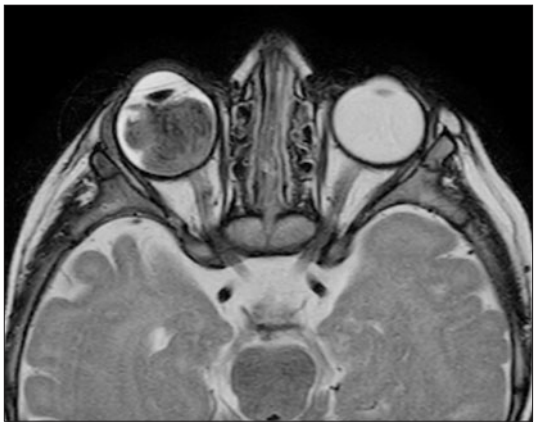

Figure 2. MRI visualization of Rb stage E (tumor is in contact with the lens)

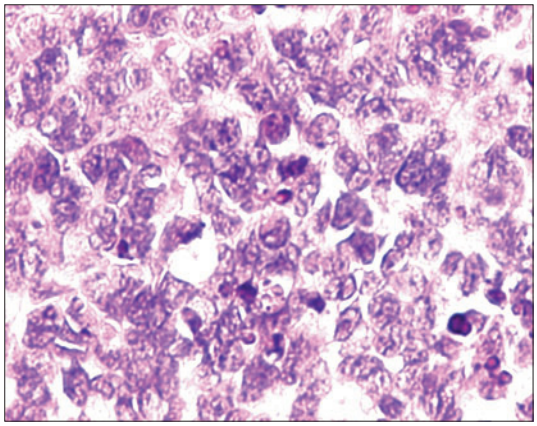

Figure 3. HE coloration with cell mitosis and apoptosis. 40x magnification

Table 2. Histological examination of the enucleated eyes

	AJCC staging	Histological classification	Tumour size (cm)	Optic nerve head invasion	Optic nerve invasion	Optic nerve resection limit	Choroidal invasion
1	L0V0Pn1	pT3aNx-G3	1,7/0,9	Yes	No	Free	Yes
2	L0V0Pn0	pT1cNx-G2	2,3/1,8	No	No	Free	No
3	L0V0Pn0	pT2aNx-G2	2/1,3	No	No	Free	No
4	L0V0Pn1	pT2aNx-G2	1,9/1,4	Yes	No	Free	Yes
5	L0V0Pn1	pT3bNx-G3	2/2	Yes	No	Free	Yes
6	L0V0Pn1	pT3bNx-G3	2,5/2	Yes	Yes	Free	No
7	L1V1Pn1	pT4Nx-G3	2,3/2,2	Yes	Yes	Invaded	Yes

Table 3. IHC analysis of the enucleated eyes

	NSE	Synaptophysin	S-100	Ki67
1	Positive	Positive	Positive	80%
2	No IHC found			
3	Positive	Positive	Focal Positive	100%
4	Positive	Positive	Inconclusive	60-70%
5	Positive	Positive	Positive	90%
6	Positive	Positive	Positive	80%
7	Positive	Positive	Inconclusive	58%

cosmetic reconstruction, with normal social development and reintegration.

Two patients have received conservative treatment outside of Romania. One has had a history of unilateral Rb for 7 years and received 2 cycles of intra-arterial chemotherapy, 13 intravitreal injections, 12 sessions of cryotherapy, 8 sessions of thermotherapy, laser treatment and cerclage in the first 4 years after initial diagnosis. In addition, he received an artificial lens after lensectomy and is currently still under surveillance. He is now receiving treatment for amblyopia on this eye and currently has a 20/25 vision. The tumor presents intraretinal and vitreous calcifications and has remain stable over the course of these years. The second patient has less than 6 months from the initial diagnosis and has received one cycle of intra-arterial chemotherapy and intravitreal injections, with favorable response.

All patients with Rb history are required to perform annual check-ups and ophthalmological investigations. Apart from the bilateral case, in which the patient had deceased and the other patient that did not return for further treatment, all 8 children with unilateral tumors have had a favorable evolution with normal development. No signs of tumor activity, malignancy in the other eye or pineal gland invasion has been recorded to date.

Discussion

Early Diagnosis

The ability to perform screening for Rb using ultrasound (US) imaging in the intrauterine development of the fetus has been known since 1992, when a 21-week fetus had been identified with a large tumor protruding from the right side of the fetal face covering most of the face (10). High resolution US examination had since been useful in monitoring pregnancies with risk of fetus developing Rb, showing efficacy in identifying lesions bigger than 2 mm in size, providing a better accuracy than other examinations such as fetal magnetic resonance imaging (MRI). The latter appeared more useful in providing data regarding extraocular tumor extension (11). While US is a noninvasive method that can be done as early as 13 weeks of gestation, MRI should not be included until 34-35 weeks of gestation (12).

Early prenatal screening can be performed using invasive and non-invasive methods. Non-invasive methods utilize fetal cell free DNA found in a blood sample from the mother in order to search for new or inherited mutations. It can be performed as early as 8 weeks of gestation in order for fetal cell free DNA to a have a higher fraction in the mother's blood and provides diagnostic capabilities, Gerrish et al. showing in a clinical

study that in 15 pregnancies with history of Rb, this method offered 100% concordance with postnatal tests (13). Invasive methods can be performed trough amniocentesis or chorionic villi sampling, the procedures are surgical with an existing chance of miscarriage or other complications (14). Future parents with known history of Rb can undergo preimplantation genetic testing during in vitro fertilization, allowing them to be aware of the nature of the RB1 mutation status prior to embryo implantation (13,14).

Multiple comparative studies have shown that incipient Rb detection with early delivery have a better chance of successful treatment with possible salvage of the eye, while on term deliveries may provide more time for the tumor to grow in size and spread compromising the effectiveness of the treatment (15,16). This aspect more than justifies the necessity of prenatal genetical screening in patients with risk for developing Rb. In Romania, prenatal screening for most common genetic anomalies is mandatory and abdominal US is used to detect any fetal abnormalities. In addition, the data is corroborated with a maternal blood test at the end of the first trimester which measures the hCG and the pregnancy-associated-plasma-protein and another one during the second trimester which evaluates HCG, alpha-fetoprotein and estriol. Access to more extensive and sensitive parameters is optional. Despite the fact that both ultrasonography and prenatal screening using both invasive and noninvasive methods is universally available in Romania, none of our patients were diagnosed with Rb using prenatal US.

Optical coherence tomography (OCT) is a noninvasive examination of elements of the posterior segment. Shields et al. have successfully proven the role of OCT in diagnosis and follow up of Rb since 2004, proving it to be more useful in evaluating macular lesions and subretinal fluid than other examinations such as US (17). Since then, they managed to describe different OCT aspects regarding active and inactive Rb (18). By using OCT an earlier detection with quicker treatment initiation can be achieved and more information regarding retina and vitreous seeding, tumor regression and the status of the macula and optic nerve. In addition, other treatment side effects such as choroidal thinning can be evaluated (19). Retinal tumor growth occurs at the inner nuclear layer extending towards the photo-receptor layers, therefore highlighting the implication of the astrocytes in Rb progression. By using handheld OCT devices, new information regarding initial tumor formation and growth can be obtained and multiple studies have highlighted the increased accuracy and early detection capabilities in clinical examination of children with Rb (20-22). While OCT is routinely used in diagnosing a large number of ophthalmological pathologies in our clinic, the lack of handheld devices for neonatal screening caused for delayed diagnosis with advanced disease at presentation.

Systemic Conservative Treatment

Conservative treatment with eye preservation consisting in systemic administration of chemotherapy has been widely adopted since the 1990, and by using a combination of different drugs such as vincristine, etoposide and carboplatin it managed to provide a treatment measure against the extraocular spread of tumor cells. The treatment regimen consisted of intravenous (IVC) once a month for 6-9 months. However, the blood choroidal barrier has a small penetrability for drug exposure and only a small percentage of the circulating chemotherapeutical agents manage to reach the vitreous cavity. Therefore, different local therapies are required to address the primary tumor which mainly has a subretinal and intravitreal implantation site. In order to reach a higher drug concentration to the eye intra-arterial administration was adopted in which a microcatheter is guided to deliver the chemotherapeutical agents selectively to the ophthalmic artery, increasing by 10 times the drug quantity that reaches the eye while reducing the systemic toxicity. Normally, it consists of single or combined drug therapy delivered once a month for 3 months. It is usually performed in patients over 3 months of age and 6 kg in weight because of the small vessel caliber. IVC can be used as a bridge therapy until the child meets the required criteria. The most common used drugs are topotecan and melphalan, the same as for intra-arterial administration. The number of injections varies depending on the response and the toxicity (23,24).

Ophthalmological Conservative Treatment

While the previous methods have been proven effective in accumulating the drug at the retinal pigmented epithelium and choroidal level, other methods are required for additional tumor management. Intravitreal chemotherapy can be used to address retinal and vitreous seeding in which a mean of 4-5 injection cycles are introduced

every 2-4 weeks, while intracameral administration is used to address aqueous seedings, the last station in tumor spreading. Focal therapies such as cryotherapy or transpupillary thermotherapy can be used in order to consolidate the effects of chemotherapy, while external beam radiation therapy and brachytherapy are rarely used because of their major side effects (19,25). Despite conservative treatment not being recommended for E stage Rb, tumor location and the relationship with surrounding structures allowed for the two patients from our study to benefit from it.

Radical Surgery

Enucleation is the safest and most used method of treating Rb, especially in patients with advanced disease. The use of conservative treatment has increased the chances of eye salvaging techniques, with enucleation being reserved for refractory cases. In developing countries, due to late presentation usually with stage D and E at diagnosis, it still holds as the first line treatment with a 5-year survival rate >90% (9,26). In our research patients showed an 85% survival rate after enucleation, but this may be caused by the small number of cases that were diagnosed.

Quality of Life (QoL)

Quality of life (QoL) in Rb children with history of enucleation has become a global concern. In a study from the Netherlands, van Dijk et al. researched the QoL of these children compared to age-appropriate reference group and their parents' perception upon it. The results were that children were not that different regarding QoL, girls having a better emotional development than the reference group, and boys having no difference between groups. Age had a negative impact on the psycho social well-being, younger patients perceiving themselves as happier and apparently presenting a closer relationship with their parents. Despite this, the parents perceived their children's QoL to be relatively poorer (27). In our findings regarding children with severe amblyopia and their parents, the latter tend to perceive their children's QoL to be higher and are less preoccupied by it or their school results (28). QoL may be different depending also on socio-economic and cultural factors. In a study from China, they found QoL in children with Rb to be lower than the reference group, and by comparing it to other studies, they had lower QoL than the Dutch children but higher than a different study from India. This may also occur because of treatment options, as the Dutch group included an approximate of 40% children with conservative treatment, while the Chinese group included only enucleated eye in their study (29,30). The higher QoL compared to Indian study may be due to post operative cosmetic restoration in Chinese children, all patients receiving ocular prosthesis. However, they also found a negative correlation between age of diagnosis and QoL, children un-der 18 months at diagnosis having a better QoL than those over. A different study that evaluated QoL in adults with history of Rb found that patients still have struggles with psycho-social issues following enucleation of the affected eyes even after many years (31).

The usage of ocular prosthesis is indispensable after enucleation. Different types of prosthesis have been developed over the years and while there is no ideal implant for all cases, their use has proven to increase QoL (32). In addition, the eye acts as an orbital natural expander, as the child grows, the eye stimulates the development of the orbit. Therefore, the prothesis should be adapted in order for the children to have facial symmetry when entering adulthood. All of the successfully enucleated patients from our research were provided with ocular prosthesis and cosmetic reconstruction when required, consisting in progressive enlargement of the ocular prosthesis and adaptation to the sur-rounding tissue for symmetrical orbital development and facial appearance. With good patient care and regular check-ups and correcting visual and cosmetic impairments, patients can learn and attend a normal education system. Even those requiring low-vision aids, in the presence of normal intellectual development are able to access universities and follow up on their wanted socio-professional orientations.

The need for family planning and genetic testing keeps increasing. In developed and developing countries families tend to have under two children, and therefore should have as many tools as possible in identifying and managing issues regarding their future off-spring. The global retinoblastoma presentation and analysis by national income level found that 49.1% of new Rb cases originate from low-income countries with an advanced disease stage at first presentation at an older age. They proposed the investigation of other factors that may be associated with advanced disease in these countries as age may not be the only factor involved. This may be true for our

patients as well, as all children had advanced E stage disease at initial diagnosis, having between 1 and 5 years of age (33).

Prenatal genetic Rb screening is available, however not everybody has the access or means to it. This is unfortunately available for all cases of Rb, as our 10 cases did not present any data of genetic testing during their ophthalmological follow ups. While other countries have benefited from reports of incidence and survival rate of Rb in Europe for many years now (34,35), we still have unreported cases that have not been the object of any centralized data gathering.

Based on data from the most recent national census the North-Eastern region of Romania should reach 28.554 newborn children per year. Our 10-year analysis provided 10 cases averaging 1 case of newly identified Rb per year. These data suggest that the incidence of Rb in our region has a rate of 1:28.554, while cited data report 1: 15 000 – 1: 20 000 per child birth. Our lower incidence could result from the presentation of these children to other centers across the country.

Therefore, the need for a unified register for following up and understanding the different varieties in pediatric cancers has never been greater.

Future Directions

With the development of promising new non-chemotherapeutical treatment types that focus on gene therapy and oncolytic virus treatments, patients could receive better tumor control with less systemic toxicity and higher chances for eye preservation (36,37). In addition, the combination of existing therapies with potential agents with antitumoral enhancing properties such as coenzymes may relieve additional toxicity and offer new treatment regimen (38). Therefore, early Rb diagnosis and genetic testing is required in order for a patient to be able to benefit from such treatments.

Study Limitations

A limit of our study relies in the low number of cases and only one investigated center. Despite the fact that the evidence is from the only major pediatric ophthalmology center from northeastern Romania, the 10 reported cases make up for around 12% of all Rb cases in the entirety of Romania, where around 8 new cases should be diagnosed every year. To the best of our knowledge, these patients have not been included in any other study or database regarding Rb incidence in Romania and this paper offers insight of a previously unreported center, treatment methods, paraclinical investigations used for positive diagnosis and patient survival rate. The retrospective nature represents another limitation of our study.

The need for new genetic testing centers with larger public availability is required as we hope to obtain data regarding our patient's genetic profile and offer guidance to high-risk patients by selecting those with necessary prenatal genetic testing, focusing on ocular modifications during prenatal US and call for regular ophthalmological check-ups after birth.

The few patients that underwent these new measures have undergone numerous financial and physical burdens having to search for them in different countries with specialized treatment centers and follow up at them for many years. Analyzing and comparing quality of life between groups and the impact the constant travels to centers in foreign countries has on the psychosocial development in these children and their parents should offer new insights into how we attend our patients.

Conclusions

Retinoblastoma is the most common ocular tumor found in children. Despite the progress of treatment in Rb around the world, developing countries still lack the ability to gather data and form unified country registries for managing and monitoring the incidence of Rb. In our 10-year analysis all children had an initial presentation with disease stage E, which highlights the need to intensify screening measures in infants in order to be able to diagnose this disease at earlier stages. Therefore, the lack of proper genetic testing makes us unable to report how many tumors had germline or developed somatic mutations and to provide patients adequate information regarding the risk of their off-spring inheriting Rb1 gene mutations.

Unfortunately, enucleation remains the primary treatment method for Rb in Romania, despite access to conservative eye saving treatment measures.

Author's Contributions

VCD, CFC, and CMB contributed to the study conception and design. VCD, CAS and IAP contributed to the acquisition of data. The

statistical analysis and overall interpretation of data was performed by VCD and CMB. VCD contributed to manuscript drafting. CFC and CMB contributed to the critical revision of the manuscript.

Conflict of Interest

All authors declare that they have no conflict of interest.

Ethical Statement

This study was performed in accordance with tenets of the Declaration of Helsinki, and all procedures were approved by the "Sf. Spiridon" Emergency Clinical Hospital ethics committee (Approval no. 65/19.08.2024). Informed consent was obtained from the parents of all subjects involved in the study, during hospitalization.

References

1. Yao Y, Gu X, Xu X, Ge S, Jia R. Novel insights into RB1 mutation. Cancer Lett. 2022;547:215870.
2. Kaewkhaw R, Rojanaporn D. Retinoblastoma: Etiology, Modeling, and Treatment. Cancers (Basel). 2020;12(8):2304.
3. Tiutiuca C, Voicu D, Brujbu I, Macovei L, Ciupilan C, Bogdanici C, et al. Malignant Tumors of the Eyeball and its Appendixes. Rev. Chim. 2016;67(8): 1641-1645.
4. MacCarthy A, Draper GJ, Steliarova-Foucher E, Kingston JE. Retinoblastoma incidence and survival in European children (1978–1997). Report from the Automated Childhood Cancer Information System project. Eur J Cancer. 2006; 42(13):2092-102.
5. Gatta G, Ferrari A, Stiller CA, Pastore G, Bisogno G, Trama A, et al. Embryonal cancers in Europe. Eur J Cancer. 2012;48(10):1425-33.
6. Stacey AW, Bowman R, Foster A, Kivelä TT, Munier FL, Cassoux N, et al. Incidence of Retinoblastoma Has Increased: Results from 40 European Countries. Ophthalmology. 2021;128(9):1369-1371.
7. López López JC, Fernández Alonso N, Cuevas Álvarez J, García-Caballero T, Pastor Jimeno JC. Immunohistochemical assay for neuron-specific enolase, synaptophysin, and RB-associated protein as a diagnostic aid in advanced retinoblastomas. Clin Ophthalmol. 2018;12:1171-1179.
8. Das D, Bhattacharjee K, Barthakur S, Tahiliani P, Deka P, Bhattacharjee H, et al. A new rosette in retinoblastoma. Indian J Ophthalmol. 2014;62(5):638-41.
9. Dimaras H, Corson TW, Cobrinik D, White A, Zhao J, Munier FL, et al. Retinoblastoma. Nat Rev Dis Primers. 2015;1:15021.
10. Maat-Kievit JA, Oepkes D, Hartwig NG, Vermeij-Keers C, Kamp ILV, Kamp JJPVD. A large retinoblastoma detected in a fetus at 21 weeks of gestation. Prenat Diagn. 1993;13(5):377-84.
11. Paquette L, Miller D, Jackson H, Lee T, Randolph L, Murphree A, et al. In utero detection of retinoblastoma with fetal magnetic resonance and ultrasound: initial experience. AJP Rep. 2012;2(1):55-62.
12. Staffieri SE, McGillivray G, Elder JE, Bristowe A, Cole S, McKenzie JD, et al. Managing fetuses at high risk of retinoblastoma: lesion detection on screening MRI. Prenat Diagn. 2015;35(2):174-8.
13. Gerrish A, Bowns B, Mashayamombe-Wolfgarten C, Young E, Court S, Bott J, et al. Non-Invasive Prenatal Diagnosis of Retinoblastoma Inheritance by Combined Targeted Sequencing Strategies. J Clin Med. 2020;9(11):3517.
14. Rodriguez A, Kelley C, Patel A, Ramasubramanian A. Prenatal Diagnosis of Retinoblastomas: A Scoping Review. Int J Gen Med. 2023;16:1101-1110.
15. Soliman SE, Dimaras H, Khetan V, Gardiner JA, Chan HSL, Héon E, et al. Prenatal versus Postnatal Screening for Familial Retinoblastoma. Ophthalmology. 2016; 123(12):2610-2617.
16. Toi A, Sutherland J, Gallie B, Gardiner J, Sermer M. Evaluation of the fetus at risk for retinoblastoma: what is the role of prenatal ultrasound? Ultrasound in Medicine and Biology. 2003;29(5):S137.
17. Shields CL, Shields JA. Diagnosis and management of retinoblastoma. Cancer Control. 2004;11(5):317-27.
18. Shields C, Manalac J, Das C, Saktanasate J, Shields J. Review of spectral domain-enhanced depth imaging optical coherence tomography of tumors of the retina and retinal pigment epithelium in children and adults. Indian J Ophthalmol. 2015;63(2):128-32.
19. Munier FL, Beck-Popovic M, Chantada GL, Cobrinik D, Kivelä TT, Lohmann D, et al. Conservative management of retinoblastoma: Challenging orthodoxy without compromising the state of metastatic grace. "Alive, with good vision and no comorbidity". Prog Retin Eye Res. 2019 Nov:73:100764.
20. Welch RJ, Rao R, Gordon PS, Say EAT, Shields CL. Optical Coherence Tomography of Small Retinoblastoma. Asia Pac J Ophthalmol (Phila). 2018; 7(5):301-306.
21. Nadiarnykh O, McNeill-Badalova NA, Gaillard M, Bosscha MI, Fabius AWM, Verbraak FD, et al. Optical coherence tomography to image active and inactive retinoblastomas as well as retinomas. Acta Ophthalmol. 2020;98(2):158-165.
22. Soliman SE, VandenHoven C, MacKeen LD, Héon E, Gallie BL. Optical Coherence Tomography-Guided Decisions in Retinoblastoma Management. Ophthalmology. 2017;124(6):859-872.
23. Shields CL, Lally SE, Leahey AM, Jabbour PM, Caywood EH, Schwendeman R, et al. Targeted retinoblastoma management: when to use intravenous, intra-arterial, periocular, and intravitreal chemotherapy. Curr Opin Ophthalmol. 2014; 25(5):374-85.
24. Zhou M, Tang J, Fan J, Wen X, Shen J, Jia R, et al. Recent progress in retinoblastoma: Pathogenesis, presentation, diagnosis and management. Asia Pac J Ophthalmol (Phila). 2024;13(2):100058.
25. Ancona-Lezama D, Dalvin LA, Shields CL. Modern treatment of retinoblastoma: A 2020 review. Indian J Ophthalmol. 2020;68(11):2356-2365.
26. Zhao J, Feng Z, Leung G, Gallie BL. Retinoblastoma Survival Following Primary Enucleation by AJCC Staging. Cancers (Basel). 2021;13(24):6240.
27. van Dijk J, Huisman J, Moll AC, Meeteren AYNSv, Bezemer PD, Ringens PJ, et al. Health-related quality of life of child and adolescent retinoblastoma survivors in the Netherlands. Health Qual Life Outcomes. 2007;5:65.
28. Bogdănici ST, Costin D, Bogdănici CM. Quality of life for amblyopic children and their parents. Rev Med Chir Soc Med Nat Iasi. 2015;119(1):214-20.
29. Zhang L, Gao T, Shen Y. Quality of life in children with retinoblastoma after enucleation in China. Pediatr Blood Cancer. 2018;65(7):e27024.
30. Batra A, Kumari M, Paul R, Patekar M, Dhawan D, Bakhshi S. Quality of Life Assessment in Retinoblastoma: A Cross-Sectional Study of 122 Survivors from India. Pediatr Blood Cancer. 2016;63(2):313-7.
31. Banerjee SC, Pottenger E, Petriccione M, Chou JF, Ford JS, Sklar CA, et al. Impact of enucleation on adult retinoblastoma survivors' quality of life: A qualitative study of survivors' perspectives. Palliat Support Care. 2020; 18(3):322-331.
32. Costea CF, Bogdanici CM, Carauleanu A, Dimitriu G, Sava A, Dumitrescu N, et al. Updates of Ocular Prostheses. A review of biomaterials and design in anophthalmic socket. Rev. Chim. 2019;70(1):239–244.
33. Fabian ID, Abdallah E, Abdullahi SU, Abdulqader RA, Adamou Boubacar S, Ademola-Popoola DS, et al. Global Retinoblastoma Presentation and Analysis by National Income Level. JAMA Oncol. 2020;6(5):685-695.
34. Seregard S, Lundell G, Svedberg H, Kivelä T. Incidence of retinoblastoma from 1958 to 1998 in Northern Europe: advantages of birth cohort analysis. Ophthalmology. 2004;111(6):1228-32.
35. MacCarthy A, Birch JM, Draper GJ, Hungerford JL, Kingston JE, Kroll ME, et al. Retinoblastoma: treatment and survival in Great Britain 1963 to 2002. Br J Ophthalmol. 2009;93(1):38-9.
36. Pascual-Pasto G, Bazan-Peregrino M, Olaciregui NG, Restrepo-Perdomo CA, Mato-Berciano A, Ottaviani D, et al. Therapeutic targeting of the RB1 pathway in retinoblastoma with the oncolytic adenovirus VCN-01. Sci Transl Med. 2019;11(476):eaat9321.
37. Schaiquevich P, Francis JH, Cancela MB, Carcaboso AM, Chantada GL, Abramson DH. Treatment of Retinoblastoma: What Is the Latest and What Is the Future. Front Oncol. 2022;12:822330.
38. Upreti S, Sharma P, Sen S, Biswas S, Ghosh MP. Auxiliary effect of trolox on coenzyme Q10 restricts angiogenesis and proliferation of retinoblastoma cells via the ERK/Akt pathway. Sci Rep. 2024;14(1):27309.