OFTÁLMICA
Asociación Guatemalteca de Oftalmología

Revista Oftálmica
ISSN 2791-2787
www.revistaoftalmica.org
Asociación Guatemalteca de Oftalmología
https://doi.org/10.56172/oftalmica.v20i.20

Vol. 20
Enero – Junio
2021

MULTIDISCIPLINARY MANAGEMENT OF RETINOBLASTOMA: THE EXPERIENCE OF MEXICO

David Ancona-Lezama, M.D. [1], *Daniela E. Gómez-Elizondo, M.D.* [1], *Daniel Bastán-Fabián* [1], *José A. Figueroa-Sánchez, M.D.* [2], *Francisco J. Rivera-Ortegón, M.D.* [3], *Juan H. Páez-Garza, M.D.* [1], *Leslie M. Thompson-García, M.Sc.* [4], *Andrea Rangel-Padilla, M.D.* [1], *Sara González-Godínez, M.D.* [1], *Dione Aguilar-Y-Méndez, M.D.* [4], *Rocío A. Villafuerte-De-La-Cruz, M.D.* [5], *Homero D. Sandoval-Alfaro, M.D.* [3], *Melissa Rodríguez- Villareal, M.Sc.* [3], *Caroline Guerrero-De-Ferrán, M.D.* [1], *Leslie V. Uribe-Ortiz, M.D.* [3], *Erik E. Pérez-Ramos, M.D.* [4], *Cecilia Crisóstomo-Aguilar, L.P.* [1]

From the 1 Institute of Ophthalmology and Visual Sciences, Tecnologico de Monterrey, Mexico, the 2 Institute of Neurology and Neurosurgery, Tecnologico de Monterrey, Mexico, 3 Private Practice, the 4 Institute of Oncology, Tecnologico de Monterrey, Mexico, and 5 Escuela de Medicina y Ciencias de la Salud, Tecnologico de Monterrey, Mexico.

No support or funding was provided for the creation of this manuscript. David Ancona-Lezama, M.D., has had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Inquiries to David Ancona-Lezama, M.D., Institute of Ophthalmology and Visual Sciences, Tecnologico de Monterrey, Mexico, Tel: +52 (81) 8888-0555, Fax: +52 (81) 8888-0555, Email: davidancona@medicos.tecsalud.mx

KEYWORDS:

Eye | Retinoblastoma | Multidisciplinary | Pediatric | Oncology Diagnostic | Treatment

INTRODUCTION

Retinoblastoma is a tumor that accounts for approximately 3% of cancers in children younger than 15 years, with 95% being diagnosed before age 5. It is usually confined to the eye, resulting in a survival rate that ranges between 30 - 97%, being over 97% in high-income countries (HICs).[1,2] The treatment of retinoblastoma is complex and requires a multidisciplinary approach to achieve the main goals of patient survival, ocular globe preservation, and optimization of visual function.

'Multidisciplinary management' is a term used in medicine to describe a treatment planning approach that includes a coordinated group of doctors and other healthcare professionals, experts in different disciplines.[3] In retinoblastoma, this team of experts includes ophthalmologists, pediatric oncologists, ocular pathologists, geneticists, endovascular neurosurgeons or neurointerventional radiologist, radiation oncologists, and mental health experts to ensure the best possible care.

A cancer diagnosis is undoubtedly a stressful event for the patient and family, especially if the patient is a child. It usually requires many family adjustments to attend frequent medical visits and hospitalizations, subsequently leading to time away from their everyday life and duties. Once treatment is over, families have to transition again to their pre-cancer lives and find a new 'normal' that will require regular medical visits and evaluations to cope with the disease's aftereffects.

Psychological care of retinoblastoma patients and their families play an important role in multidisciplinary management. Several reports have suggested that parents experience elevated levels of stress associated with the initial diagnosis.[4,5] This disease has been described as overwhelming, especially for parents of children that require enucleation.[4,5] Some studies report that parents with visually impaired children undergo more stress than parents of children with typical development.[6] Therefore, it is essential to include mental health interventions in the multidisciplinary management of these cases, both with the patient and their families, as the caretakers' stress may influence child outcomes, including cognitive development.[7]

Multidisciplinary management of cancer is a common approach in HICs like the United States of America. Patients usually have access to intensive treatments, cooperative trials, and molecular diagnosis that facilitates targeted therapies that positively contribute to an increased survival rate that approaches 98–99%.[1,2] The ability to carry out higher screening levels and virtual freedom from restrictions regarding the best available treatment options, including quality multidisciplinary management, permits curation to become the ultimate focus, with easier access to long-term follow-up.

Sadly, approximately 80% of the newly diagnosed childhood cancer cases each year occur in developing countries.[8] In low- and middle-income countries (LMICs), adequate treatment of retinoblastoma remains a major challenge as patients often present with advanced disease. Several factors contribute to this challenge: the impaired access to healthcare, the scarcity of human resources, the unavailability of medications or procedures, inadequate infrastructure, poor education, and the lack of support from government and international nongovernmental organizations. Therefore, the sophisticated multidisciplinary care that these patients require is not always available. These limitations contribute to the higher mortality rate registered in LMICs. In Asia and Africa, between 40 and 70% of children with retinoblastoma die, compared with some only 3-5% in some HICs.[9]

9.1 to 16%

The retinoblastoma mortality rate ranges.

In Mexico, cancer is the leading cause of death in children age 5-9 years.[10] The retinoblastoma mortality rate ranges from 9.1 to 16%, resembling those in most Latin American countries.[10] In Mexico, the treatment of retinoblastoma remains a challenge due to the uneven distribution of ophthalmologists among Federal States. Only 15 certified ophthalmologists exist in the sparsest State, while 894 exist in the most plentiful.[11] The number of surgical centers also varies among States, ranging from 14 per 100,000 people in the states with the highest income to 4 per 100,000 in the states with the lowest income.[12] There is insufficient data on the number of institutions that treat patients with retinoblastoma. However, records show only 183 board-certified pediatric oncologists and only six ophthalmologists with formal ocular oncology training are available in the whole country.[13] Specific therapies used in the treatment of retinoblastoma, like intra-arterial chemotherapy, are currently available only in a few certified centers in the country. In our center, the administration of sophisticated multidisciplinary care, including targeted therapies that these patients require, is available.

DIAGNOSTIC APPROACH

The ideal path towards retinoblastoma cure begins with a thorough history. The first contact clinician, either telemedicine center, nurse, general practitioner, pediatrician, ophthalmologist, pediatric oncologist, pediatric ophthalmologist, retina specialist, or ocular oncologist, must first investigate the time onset of symptoms. When this is not possible, the clinician must query about the first time any parent registered a shift in the child's development. Despite that this guards no accurate correlation with disease severity, a distant date could infer a diagnostic delay and therefore advanced stage. Previous exams, blood work, imaging, and interventions should also be recorded.

Pre- and perinatal history is equally relevant. Data should include gestational age at birth, birth weight, delivery technique, and complications, as well as any abnormalities observed in control ultrasounds (structural or developmental), at eye screening, birthmarks, or malformations, especially those associated with 13q Deletion Syndrome.[14]

Retinoblastoma is caused by biallelic inactivation of the retinoblastoma susceptibility gene RB1 in 13q14 locus; the first genetic event could be hereditary (40%) or non-hereditary (60%); the second genetic event occurs at somatic level (embryonic retinal cells).

A complete examination should not only include the child, but also both their biological parents and siblings, as sometimes, spontaneously regressed retinoblastoma, arrested retinoblastoma, or retinoma/retinocytoma could be incidentally encountered.[15]

Deliberate queries pertinent to retinoblastoma's most distinguishable simulating conditions also termed 'pseudoretinoblastoma' should be addressed.[16] Such is the case of exposure to pets (infectious granuloma), prematurity or administration of supplemental oxygen (retinopathy of prematurity), obstetric trauma (vitreous hemorrhage), CHARGE (coloboma), PHACE syndrome (morning glory disc), neurofibromatosis (hamartoma of the retina and RPE), tuberous sclerosis (retinal astrocytic hamartoma), other genetic disorders (retinal detachment), sepsis (endogenous endophthalmitis), family history of congenital cataract (congenital cataract), galactosemia (congenital cataract), among many others.[17,18]

After a full detailed history is recorded, the initial office examination must include visual acuity assessment, subjective and cycloplegic refraction of both eyes, clinical photography, strabismus evaluation, tonometry, slit-lamp examination, and full-dilated eye examination. Ideally, an ultrasound and widefield fundus photography must be performed in-office. The clinician will attempt to confirm or discard retinoblastoma and initially staged it by the International Classification of Retinoblastoma (for intraocular staging). It is important to remember that the classification will be reassessed for a final staging following the availability of the full systemic workup.

An initial MRI should be scheduled at diagnosis. Given its superior soft-tissue contrast, MRI is preferred over CT scan in detection of tumor extent and metastatic risk factors. Additionally, CT exposes the child to unnecessary radiation that, in the case of a germline mutation, could add-up to the radiation burden. It is important to recall that a radiation accumulation of as little as 5 Gy over the course of a lifespan in a retinoblastoma patient with germline mutation carries an elevated risk for radiation-induced sarcoma.[19]

Diffuse infiltrative retinoblastoma should also be considered due to its peculiar clinical characteristics, including older age, female sex, pseudoinflammation, absence of mass, retinal detachment in cinnamon-roll configuration, among others.[20]

TREATMENT APPROACH

MANAGEMENT OF RETINOBLASTOMA

As we know, the management of retinoblastoma (Rb) depends largely on the stage of the tumor, the coexistence of extraocular factors, whether the tumor comes from a germline mutation, the family support network, and, finally, the availability of resources. If the patient has a positive family history for retinoblastoma, one should suspect a germline mutation, with all the problems such a tumor would entail. All patients should get a simple and contrast-enhanced MRI of the brain and orbits. [21]

A comprehensive and clinically useful staging scale is the International Classification of Retinoblastoma (ICRB). Table 1 summarizes this scale (Table 1). This classification scheme focuses on the size, location, seeding, and invasion of the tumor. Depending on the group where the tumor lies, the clinician can devise a treatment plan. [22,23]

GROUP	FEATURES
A	Rb ≤3 mm in basal diameter or thickness
B	Rb >3 mm in basal diameter or thickness OR Tumor location ≤3 mm from foveola OR Tumor location ≤1.5 mm from optic disc OR Tumor-associated subretinal fluid ≤3 mm from tumor margin
C	Rb with subretinal seeds ≤3 mm from tumor OR Rb with vitreous seeds ≤3mm from tumor OR Rb with subretinal and vitreous seeds ≤3 mm from tumor
D	Rb with subretinal seeds >3 mm from tumor OR Rb with vitreous seeds >3 mm from tumor OR Rb with subretinal and vitreous seeds >3 mm from tumor
E	Rb occupying >50% of the globe OR Neovascular glaucoma OR Opaque media OR Invasion of optic nerve, choroid, sclera, orbit, and/or anterior chamber

INTRAVENOUS CHEMOTHERAPY (IVC)

Since its inception in the early 1990s, IVC has remained a staple in Rb management. This modality of treatment consists of 2-4 chemotherapeutic agents which are administered monthly via a central or peripheral catheter for 6-9 cycles. The most widespread regimen consists of vincristine, etoposide, and carboplatin; this treatment is coined as 'VEC'. Focal consolidation with thermotherapy, particularly cryotherapy, can be utilized in conjunction with IVC to enhance drug availability, especially when given within 48 hours of thermal disruption. [21,24,25]

Indications for IVC include bilateral disease, confirmed germline mutation, positive family history of Rb, and suspicion of optic nerve or choroidal invasion. IVC also plays a role in preventing long-term secondary cancers, metastases, and pineoblastoma. Another indication implies patients whose body weight is under 6 kilograms and who are awaiting intra-arterial chemotherapy (IAC); this is known as "bridge therapy". In the case of enucleation, the tumor should be analyzed by histopathology. If high-risk features (such as post-laminar optic nerve invasion, massive choroidal

invasion (>3 mm in diameter), or extraocular extension) are present, high-doses of IVC should be given to prevent metastases. All patients undergoing IVC should receive prophylaxis for Pneumocystis jirovecii. [21,25]

Common side effects of IVC include transient alopecia, cytopenia, and fever. Systemic toxicity, if present, is usually mild. Nausea, emesis, and constipation are prevalent side effects as well, but they can be medically managed. Other side effects, although rare, include renal toxicity, secondary acute myelogenous leukemia, and infertility. The latter is more common in males if melphalan is added to the treatment plan, more so if the cumulative dose reaches 140 mg/m^2. [21]

INTRA-ARTERIAL CHEMOTHERAPY (IAC)

IAC was introduced in 1990 by Akihiro Kaneko to treat Rb when it was confined to the eye. Nowadays, IAC is an angular stone in the management of unilateral intraocular Rb. IAC achieves ten times the chemotherapy dose delivered to the eye in comparison to IVC. The treatment usually consists of 1-3 drugs administered once a month for three sessions. This option is complex and usually expensive due to the need for collaboration with a neurosurgeon or interventional neuroradiologist. This monetary impediment is why IAC is not widely employed in LMICs. [21,24,25]

When the tumor is in group B and C of the ICRB classification system, monotherapy with melphalan (5 mg) is sufficient. Nevertheless, with more advanced (groups D and E) or refractory disease, dose-escalation or addition of topotecan or carboplatin might be needed. It is worth mentioning that carboplatin has been used less frequently because of its high ophthalmic toxicity rates. Indications for IAC include first line and globe salvaging therapy. It is used as primary therapy for non-germline, unilateral, group B-E Rb, as well as secondary therapy for unilateral or bilateral advanced refractory disease. Another indication is the treatment for subretinal and vitreous seeds, particularly when they are adjacent to the retina, and rescue therapy for recurrence after previous IAC. The downside of IAC is that it hasn't been demonstrated to be effective against metastases or pineoblastoma prevention. [21,24,25]

Despite the method of highly localized delivery of the agents, there have been cases of systemic toxicity with IAC. One such side effect is neutropenia, which has been reported in 12% of patients. Other, less common, side effects include femoral artery occlusion with blue toe syndrome, carotid artery dissection, stroke, and death. Periocular side effects are more common but seldomly severe, these are periorbital edema, cutaneous hyperemia, madarosis, blepharoptosis, and extraocular dysmotility. Ophthalmic vascular side effects include choroidal occlusive vasculopathy, retinal artery occlusion, ophthalmic artery spasm or occlusion, and vitreous hemorrhage. Also, rhegmatogenous retinal detachment has been reported in 8-16% of cases treated with primary IAC, this may be due to rapid tumor regression. [21,24,25,26]

INTRAOCULAR CHEMOTHERAPY (IOC)

IOC can be divided into three types: intravitreal (IvitC), precision intravitreal (p-IvitC), and intracameral (IcamC). IvitC is useful in combination with IAC for the treatment of vitreous seeds but it is not used as monotherapy. Contraindications for this therapy include the presence of tumor or vitreous seeds at the site of needle entry, invasion of the pars plana, and anterior chamber seeding. The main agents in IvitC are melphalan and topotecan, and they can be used in combination. These are instilled inside the vitreous, and the eye is shaken for 30 seconds to ensure adequate distribution. The dosage of 20-30 µg every 2-4 weeks is sufficient to control vitreous seeds while avoiding unwanted side effects, which are cataract, vitreous and subretinal hemorrhage, ocular hypotony, phthisis bulbi, salt-and-pepper retinopathy, anterior segment toxicity, and many more. Precision intravitreal chemotherapy (p-IvitC) differs from the latter in that it is injected under direct visualization and that the eye is not jiggled, but rather the head is positioned in a preferred orientation following injection. [21,24,25]

Intracameral chemotherapy (IcamC) is meant to provide adequate drug availability in the anterior chamber. Prior to its creation, aqueous seeding was an indication for enucleation or anterior chamber radiotherapy. This treatment consists of melphalan (15-20 µg/0.05 mL) or topotecan (7.5 µg/0.015 mL) divided into thirds and delivering 1/3 of the dose to the anterior chamber and the remainder to the posterior chamber. Side effects include iris heterochromia and progressive cataract, but this might be ameliorated with the usage of topotecan instead of melphalan. [21,24,25]

FOCAL THERAPIES

The most frequently used are cryotherapy and transpupillary thermotherapy (TTT). These are often used for consolidation of the tumor in addition to IVC and IAC and are usually performed under indirect ophthalmoscopy. Cryotherapy indications include treatment of small tumors and foci of subretinal or preretinal seeds, although this procedure is rarely used as monotherapy. TTT is performed with a diode laser and is also used in conjunction with chemotherapy for small tumors <3 mm in diameter and <2 mm in thickness. Multiple TTT sessions are required, usually 2-6 at 4-week intervals and indocyanine green can enhance its effects. Side effects common to both treatments include chorioretinal scarring and diminished visual acuity to some degree. [21,25]

EXTERNAL BEAM RADIOTHERAPY (EBRT)

This treatment was used as globe salvage therapy prior to the use of modern IVC. Nowadays, it retains its usefulness in the treatment of extraocular extension, orbital recurrence, and positive optic nerve margin post-enucleation. Combination of EBRT and IVC has been reported to successfully achieve control in 71% of cases. However, radiation side effects can be serious and can range from dry-eye syndrome and cataract to secondary primary tumors in the areas exposed to radiation. The latter has been reported in up to 53% of patients by the time they are 50 years of age, and the most common tumor is osteosarcoma followed by other bone tumors and soft tissue sarcomas, melanoma, and epithelial tumors of the breast, bladder, colon, and kidneys, just to name a few. [21,24,25]

PLAQUE RADIOTHERAPY

Also known as brachytherapy, this modality of treatment is used as secondary treatment for medium-sized chemoresistant tumors, regardless of the presence (or absence) of vitreous or subretinal seeds, with recurrence after IVC or IAC. Iodine-125 is the most used isotope and the dose is designed to deliver 35-40 Gy. It takes 2-4 days to deliver the intended dose and it avoids many side effects commonly seen in EBRT, especially the development of new tumors. Side effects include cataract, radiation maculopathy and/or papillopathy, and vitreous hemorrhage. Intravitreal anti-VEGF antibodies can be used to treat macular edema following brachytherapy, but this should be delayed until confirmed tumor regression to avoid extraocular extension. [21,24,25]

ENUCLEATION

Enucleation remains an important staple of treatment. This is particularly true with group E tumors, poor visualization of the tumor due to hemorrhage, extraocular extension, invasion of the optic nerve or choroid, or resistant tumors that did not respond to other salvaging modalities. Complications include infections, as well as giant papillary conjunctivitis due to the prosthesis being in contact with the area. Because of the important functional, physical, and psychological effects that enucleation can prompt, prosthetics should be promoted as soon as possible following the first six weeks. [21,24,25]

PATHOLOGY WORKUP

Diagnostic vitreous tap or vitrectomy is generally not encouraged. When enucleation is performed, the entire globe must be analyzed by pathology. Current consensus guidelines for adequate handling of the specimen recommend obtaining four main blocks: one block for the central pupil-optic nerve (PO) section containing the optic nerve, tumor, and anterior chamber structures. Two blocks for the calottes (remainder of ocular tissue after obtaining the PO) in anterior-posterior segments embedded on edge to examine more choroidal surface, and one block containing the cross-section of the margin of the optic nerve, obtained before opening the eye. This last block is usually harvested directly from the surgeon in the operating room. [27]

Massive choroidal invasion (> 3 mm), focal choroidal invasion (< 3 mm), extraocular extension (beyond scleral tissue), optic nerve invasion in mm (prelaminar, laminar, retrolaminar, or tumor at the surgical margin) must be directly annotated as it carries prognosis risk and is of utmost importance for clinical decisions. [27]

MENTAL HEALTH PROGRAM

Eye cancer is a potentially overwhelming experience for a child. It is of the utmost importance to include the patient's psychological well-being throughout the treatment of retinoblastoma. Because it's more likely that the patient is a minor of less than five years old, the caregivers play an important role in the follow-up of the treatment and wellbeing of the child. After the diagnosis, a team of psychotherapists is provided for the patient and the caregivers. A therapist is fully focused on the child. Our program provides the child with an object they can identify with and, by taking care of their loyal companion, they can learn to take care of themselves. Additionally, through medical play, the child explores the common medical materials and pretends to "be"' the doctor to work through their experience of the diagnosis and treatment of retinoblastoma. Keeping the patient's experience in mind it is also important to assess the burden placed upon the caregivers of said patients, a second therapist is assigned to the caregivers to provide therapeutic companionship through the treatment and assess their own experience and impact of the diagnosis of their family member. Additionally, psychiatry attention is provided whenever needed.

FOLLOW UP

Patients should receive regular evaluations every four weeks to assess the treatment's response, screen for side effects, and continue to take part in the decision-making process. A simple and contrast-enhanced MRI of the brain and orbits should be performed every six months until the child is five years old. As for the remainder of the patient's lifespan, follow up should be individualized based on the characteristics the child presents, whether high-risk factors were present or not. It is worthwhile mentioning that most recurrences take place in the first three years after initial remission, although late-onset recurrences can occur up to 11 years after treatment. Patients should have their visual acuity evaluated with the same frequency as the general population, with exception of the ones who received radiation therapy. These patients should be evaluated more frequently in light of the fact that they experienced more incidence of cataract and orbital deformities. [21,24,25,28]

The rate of strabismus in Rb survivors is also worth mentioning. Several studies have found that this outcome is somewhat common, one of them demonstrating that 60% of their group D Rb sample size (12 out of 20 patients) had strabismus at five years of follow-up, with exotropia being the most frequently presenting variant. While this particular cohort was not very large, it is important to note that amblyopia is a serious sequela of strabismus and should be addressed accordingly. [28,29,30]

In the case of hereditary Rb, the American Association for Cancer Research (AACR) suggests implementing non-sedated exams every 2-4 weeks from birth to 8 weeks of age. From 8 weeks to 12 months of age Examination Under Anesthesia (EUA) should be performed monthly. Subsequent check-ups should be performed as follows:

- 12 to 24 months: EUA every two months.
- 24 to 36 months: EUA every three months.
- 36 to 48 months: EUA every four months.
- 48 to 60 months; EUA every six months.
- 5 to 7 years: non-sedated exams every six months.
- >7 years: non sedated exams every 1-2 years.

This surveillance regimen is intended for intraocular Rb. For trilateral Rb, an MRI of the brain and orbits should be performed at the time of diagnosis and every six months thereafter until the child is five years of age. In the case of second primary tumors, surveillance should be performed by means of patient education about risks and being mindful of new signs and symptoms. Also, patients should undergo skin examination at the time of well-child visits, and annually thereafter until 18 years of age because of the risk of melanoma. Some experts recommend whole-body MRI yearly after the child turns eight years old, but there is currently no consensus on this recommendation. [31]

The overall rate of depression and anxiety among retinoblastoma survivors is not higher than survivors of other cancers. Despite this, bilateral retinoblastoma survivors seem to have an increased fear of recurrence or secondary cancers arising from treatment. This fact reiterates the fact that physicians should not take their patients' mental health for granted. Long term psychological support is recommended for the adequate emotional and sensory-motor development of the child. Additionally, long term psychotherapy for the caregivers can provide the space to work through the adjustments that the treatment requires. Survivorship programs also exist, and patients should be encouraged to reach out to them for reassurance and amplifying their support network. [30,32,33]

CHALLENGES TO OVERCOME

The consolidation of a multidisciplinary group has presented many challenges. First and foremost, all the members of the team have to be in constant communication and aligned with the course of treatment. Our team developed a flowchart of the specialists and the order in which the patient is required to have an appointment with them. Nonetheless, there are still challenges to be addressed in regard to the coordination of agendas and overall flow of the course of treatment in order to improve the experience of the patient.

Another important challenge was the integration of a mental health program in the treatment of retinoblastoma. Our team, as healthcare professionals treating patients with cancer on a daily basis, understand the emotional impact of the diagnosis and treatment of retinoblastoma, and the importance of mental health as a fundamental part of the treatment, not only for the patient and the family's well-being but also because of the positive impact towards the medical interventions. Nonetheless, in Mexico, there's still a stigma towards mental health care as non-important or just for mental health problems, creating a resistance in the patients to seek mental health care. Our team has developed a program that includes mental health interventions in the overall treatment for retinoblastoma, but there's still a long way to go in our society towards the inclusion of mental health in hospital settings and addressing the social stigma towards psychological attention.

Undoubtedly, the synchronization of multiple specialists is a dutiful task. However, as it has grown to become the standard of care, every center aiming to treat retinoblastoma should recruit a complete and integrated task force for the patients' safety.

REFERENCES

1. *Ghisoli ML, Zage PE, Herzog C, Chevez-Barrios P, Chintagumpala M, Hurwitz RL, et al. Multidisciplinary Management of Retinoblastoma: Diagnosis, Treatment, and Future Direction. Ophthalmic Oncology. 2010;:179–99.* https://doi.org/10.1007/978-1-4419-0374-7_14
2. *Kivelä T. The epidemiological challenge of the most frequent eye cancer: retinoblastoma, an issue of birth and death. Br J Ophthalmol. 2009;93:1129–31* https://doi.org/10.1136/bjo.2008.150292
3. *NCI Dictionary of Cancer Terms. National Cancer Institute. Available: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/ multidisciplinary [Accessed 22 Dec 2020]*
4. *Ek U. Emotional reactions in parents and children after diagnosis and treatment of a malignant tumour in the eye. Child Care Health Dev. 2000;26:415–428.* https://doi.org/10.1046/j.1365-2214.2000.00159.x
5. *Hamama-Raz Y, Rot I, Buchbinder E. The coping experience of parents of a child with retinoblastoma-malignant eye cancer. J Psychosoc Oncol. 2012;30:21–40.* https://doi.org/10.1080/07347332.2011.633977
6. *Tröster H. Sources of stress in mothers of young children with visual impairments. J Vis Impair Blind. 2001;95:623–637.* https://doi.org/10.1177/0145482X0109501005
7. *Hile S, Erickson SK, Agee B, et al. Parental stress predicts func- tional outcome in pediatric cancer survivors. Psycho-Oncology 2014;23:1157–1164* https://doi.org/10.1002/pon.3543
8. *Luna-Fineman S, Barnoya M, Bonilla M, Fu L, Baez F, Rodríguez-Galindo C. Retinoblastoma in Central America: Report from the Central American Association of Pediatric Hematology Oncology (AHOPCA). Pediatric Blood & Cancer. 2011;58(4):545–50.* https://doi.org/10.1002/pbc.23307
9. *Dimaras H, Kimani K, Dimba EA, Gronsdahl P, White A, Chan HS, et al. Retinoblastoma. The Lancet. 2012;379(9824):1436–46.* https://doi.org/10.1016/S0140-6736(11)61137-9
10. *M. A. Ramirez-Ortiz, V. C. Lansingh, K. A. Eckert et al., Systematic review of the current status of programs and general knowledge of diagnosis and management of retinoblastoma. Boletın Medicodel Hospital Infantil de Mexico. 2017;74(1):41–54* https://doi.org/10.1016/j.bmhimx.2016.08.002 https://doi.org/10.1016/j.bmhime.2017.12.001
11. *Sociedad Mexicana de Oftalmología A. C. Available: https://www.smo.org.mx/directorio_medico.php [Accessed 22 Dec 2020]*
12. *Informe sobre la Salud de los Mexicanos – Diagnóstico General del Sistema Nacional de Salud. 2016, Available: https://www.gob.mx/cms/uploads/attachment/file/239410/ISSM_2016. pdf [Accessed 22 Dec 2020]*
13. *Garza-Garza LA, Ruiz-Lozano RE, Rebolledo-Méndez G, Ibarra-Nava I, Morales-Garza HJ, Ancona-Lezama D. Challenge of Retinoblastoma in Mexico in 2020: Perspectives and Solutions. Journal of Ophthalmology. 2020;2020:1–6.* https://doi.org/10.1155/2020/1953602
14. *Quélin C, Bendavid C, Dubourg C, Rochebrochard CDL, Lucas J, Henry C, et al. Twelve new patients with 13q deletion syndrome: Genotype–phenotype analyses in progress. European Journal of Medical Genetics. 2009;52(1):41–6.* https://doi.org/10.1016/j.ejmg.2008.10.002
15. *Shields CL, Shields JA, Baez K, Cater JR, De Potter P. Optic nerve invasion of retinoblastoma. Metastatic potential and clinical risk factors. Cancer. 1994;73: 692–8* https://doi.org/10.1002/1097-0142(19940201)73:3<692::AID-CNCR2820730331>3.0.CO;2-8
16. *Shields CL, Schoenberg E, Kocher K, Shukla SY, Kaliki S, Shields JA. Lesions Simulating Retinoblastoma (Pseudoretinoblastoma) in 604 Cases. Ophthalmology. 2013;120(2):311–6.* https://doi.org/10.1016/j.ophtha.2012.07.067
17. *MD MBS. Morning Glory Syndrome. American Academy of Ophthalmology. 2017. Available: https://www.aao.org/disease-review/neuro-ophthalmology-morning* -glory-syndrome [Accessed 28 Dec 2020]
18. *Bustos-Zepeda M, Ortega-Ramírez C. Catarata Congénita. Rev Hosp Gral Dr. M Gea González. 2001;4:57-60*
19. *Wong FL, Boice JD Jr, Abramson DH, Tarone RE, Kleinerman RA, Stovall M, Goldman MB, Seddon JM, Tarbell N, Fraumeni JF Jr, Li FP. Cancer incidence after retinoblastoma. Radiation dose and sarcoma risk. JAMA. 1997;278(15):1262-7*

https://doi.org/10.1001/jama.278.15.1262
https://doi.org/10.1001/jama.1997.03550150066037

20. *Ancona-Lezama D, Garza-Garza LA, Ruiz-Lozano RE, Shields CL, Villagomez-Valdez LG, De-Leija-Portilla JO. Diffuse infiltrative retinoblastoma with retinal detachment in "cinnamon-roll" configuration: a case report. J AAPOS. 2020;S1091-8531(20)30315-3.* https://doi.org/10.1016/j.jaapos.2020.10.004
21. *Ancona-Lezama D, Dalvin LA, Shields CL. Modern treatment of retinoblastoma: A 2020 review. Indian J Ophthalmol 2020;68:2356-65.* https://doi.org/10.4103/ijo.IJO_721_20
22. *Fabian ID, Reddy A, Sagoo MS. Classification and staging of retinoblastoma. Community Eye Heal J. 2018;31(101):11-13.*
23. *Shields CL, Lally SE. 10 10.1. In: Duangnate Rojanaporn, ed. 1st ed. Springer Singapore; 2019:91-99.* https://doi.org/10.1007/978-981-13-2336-2
24. *Fabian ID, Onadim Z, Karaa E, Duncan C, Chowdhury T, Scheimberg I, et al. The management of retinoblastoma. Oncogene [Internet]. 2018;37(12):1551–60. Available from:* https://doi.org/10.1038/s41388-017-0050-x
25. *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 [Internet]. 2019;73(May):100764. Available from:* https://doi.org/10.1016/j.preteyeres.2019.05.005
26. *Sarici A, Kizilkilic O, Celkan T, Gode S. Blue toe syndrome as a complication of intra-arterial chemotherapy for retinoblastoma. JAMA Ophthalmol. 2013;131(6):801-802.* https://doi.org/10.1001/jamaophthalmol.2013.1458
27. *Xavier Sastre, Guillermo L. Chantada, François Doz, Matthew W. Wilson, Maria T. G. de Davila, Carlos Rodríguez-Galindo, Murali Chintagumpala, Patricia Chévez-Barrios; Proceedings of the Consensus Meetings From the International Retinoblastoma Staging Working Group on the Pathology Guidelines for the Examination of Enucleated Eyes and Evaluation of Prognostic Risk Factors in Retinoblastoma. Arch Pathol Lab Med 1 August 2009; 133 (8): 1199–1202.* https://doi.org/10.5858/133.8.1199
28. *Pulido J. Long-term visual outcome following chemoreduction for retinoblastoma: Commentary. Evidence-Based Ophthalmol. 2006;7(2):91-92.* https://doi.org/10.1097/01.ieb.0000209779.95400.f6
29. *Fabian ID, Naeem Z, Stacey AW, et al. Long-term Visual Acuity, Strabismus, and Nystagmus Outcomes Following Multimodality Treatment in Group D Retinoblastoma Eyes. Am J Ophthalmol. 2017;179:137-144.* https://doi.org/10.1016/j.ajo.2017.05.003
30. *Nahum MP, Gdal-On M, Kuten A, Herzl G, Horovitz Y, Arush MW Ben. Long-term follow-up of children with retinoblastoma. Pediatr Hematol Oncol. 2001;18(3):173-179.* https://doi.org/10.1080/08880010151114769
31. *Kamihara J, Bourdeaut F, Foulkes WD, Molenaar JJ, Mosse YP, Nakagawa A, et al. Retinoblastoma and Neuroblastoma predisposition and surveillance. Clin Cancer Res. 2017;23(13):e98–106.* https://doi.org/10.1158/1078-0432.CCR-17-0652
32. *Ford JS, Chou JF, Sklar CA, et al. Psychosocial outcomes in adult survivors of retinoblastoma. J Clin Oncol. 2015;33(31):3608-3614.* https://doi.org/10.1200/JCO.2014.60.5733
33. *Collins MLZ, Bregman J, Ford JS, Shields CL. Depression, Anxiety, and Stress in Parents of Patients With Retinoblastoma. Am J Ophthalmol. 2019;207:130-143.* https://doi.org/10.1016/j.ajo.2019.05.020

Los autores declaran que no tienen ningún conflicto de interés. El estudio fue financiado con recursos de los autores.

Recibido: 30 de diciembre 2020
Aceptado: 12 de enero de 2021
Publicado: 6 de abril 2021

Derechos de Autor (c) 2021 David Ancona-Lezama; Daniela E. Gómez-Elizondo; Daniel Bastán-Fabián; José A. Figueroa Sánchez; Francisco J. Rivera-Ortegón; Juan H. Páez-Garza; Leslie M. Thompson-García; Andrea Rangel-Padilla; Sara González-Godínez; Dione Aguilar-Y-Méndez; Rocío A. Villafuerte-De-La-Cruz; Homero D. Sandoval-Alfaro; Melissa Rodríguez- Villareal; Caroline Guerrero-De-Ferrán; Leslie V. Uribe-Ortiz; Erik E. Pérez-Ramos; Cecilia Crisóstomo-Aguilar.

Este texto está protegido por una licencia *Creative Commons 4.0*.

Usted es libre para Compartir —copiar y redistribuir el material en cualquier medio o formato— y Adaptar el documento —remezclar, transformar y crear a partir del material— para cualquier propósito, incluso para fines comerciales, siempre que cumpla la condición de:

Atribución: Usted debe dar crédito a la obra original de manera adecuada, proporcionar un enlace a la licencia, e indicar si se han realizado cambios. Puede hacerlo en cualquier forma razonable, pero no de forma tal que sugiera que tiene el apoyo del licenciante o lo recibe por el uso que hace de la obra.

Resumen de licencia - Texto completo de la licencia