Retinoblastoma

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ABSTRACT

Retinoblastoma (RB) is the most frequent intraocular malignancy of childhood. Tumorigenesis has been firmly associated with mutations of the tumor suppressing RB1 gene, while, recently, involvement of additional genetic modifications has been illustrated. Clinically, RB is most commonly presented with leukocoria and strabismus. Imaging techniques supplement diagnosis and contribute to a more accurate tumor assessment. Several classification systems have been introduced for the purpose of planning therapeutic efforts more precisely. Current available treatment options include surgical removal, radiation, chemotherapy and focal modalities. Despite intravenous chemotherapy being the standard treatment, localized methods of administration havealso shown efficiency the past few years. Enucleation still remains a potential alternative, especially in cases with poor prospect of eye salvage. Focal therapy has been utilized mostly as a complementary treatment to chemotherapy.

Key words: Intraocular Malignancy, Leukocoria, Strabismus.

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Introduction

Scottish surgeon James Wardrop was the first to describe retinoblastoma in 1809[1]. Retinoblastoma is presented with either hereditary or non-hereditary form. It originates from retinal cells and unilateral or bilateral lesions may be observed[2]. Ocular tumors combined with a midline intracranial primitive neuroexodermatic tumor (PNET), commonly at the suprasellar or parasellar regions, are termed as trilateral retinoblastoma[3]. Occurrence of RB is more frequently reported in Asia and Africa, where birth rates are high[4]. Therapeutic efforts concentrate on both life and eye salvage, preservation of vision, as well as prevention of metastasis and secondary tumors[5].

Epidemiology

The global incidence of retinoblastoma is approximated at 1 in 16.000 to 1 in 18.000 live births with 8000 new cases expected annually[6]. In the United States and Europe 2 to 5 per million children each year are presented with this malignancy[7]. Despite the absence of predisposition based on gender or race, individuals from low- and middle- income countries have a higher incidence rate compared to those from upper income1. Two-thirds of the children are diagnosed before the age of 2 and 95% of them before the age of 5[7]. The disease is identified as hereditary in the majority of bilateral cases and in 10-15% of unilateral[8]. As surviving individuals are more prone to developing second primary tumors, these represent the major cause of morbidity amongst them[9]. External beam radiotherapy appears to contributes to this risk[10]. In 1.5-3% of unilateral cases within the first months metachronous tumors will appear at the opposite eye[11]. Trilateral retinoblastoma presents, with 5,3% in bilateral and 4,1% chance in

unilateral hereditary disease[3]. The overall survival rates are reported at 30% in Africa, 60% in Asia, 80% in Latin America reaching 95-97% at Europe and North America[4]. Only 45 cases of adult onset retinoblastoma have been reported worldwide[12].

Genetics

In 1971 Alfred G. Knudson provided an explanation for retinoblastoma by introducing the two-hit hypothesis. According to this model in hereditary retinoblastoma a germline mutation is required, representing the first hit, along with a second somatic mutation, the second hit. In the case of non-hereditary retinoblastoma, two somatic mutations cause the tumorigenesisoccurrence. The majority of bilateral cases is of hereditary nature, while only 10-15% of unilateral tumors have heritable traits. Following an autosomal dominant pattern of inheritance, the penetrance of hereditary retinoblastoma reaches 90%[8]. Germline mutations can be either inherited or occur as a de novo mutation. The probability of a de novo mutation resulting in mosaicism should be taken into account[13].

RB1 gene is located in chromosome 13q14 and translates into pRB, a 928 amino-acid protein[14]. It is associated with several tumors including retinoblastoma, osteosarcoma, small cell lung cancer, breast cancer and pancreatic cancer. RB1 acts as a tumor suppressing gene, which suppresses E2F transcription factors. The hyperphosphorylated pRB represses the promoters of the genes correlating to E2F transcription factors, hence, reversely inhibiting the advancement of the cell cycle. In the presence of signals promoting mitosis the cyclin-dependent kinases (CDKs) hyperphosphorylate pRB in order to progress the cell cycle from G1 to S phase[15].

Retinoma, a benign retinal tumor, has both RB alleles inactivated, too. This illustrates that additional, either genetic or epigenetic, modifications are required for the development of the malignancy[16]. Mutations on BCOR gene, a corepressor of transcription, display the second highest frequency following RB1[17]. Genomic gains are also observed at 1q, 2p and 6p along with 16q loss[18]. The p53 pathway is related to RB either with mutations in TP53 gene or inactivation of the pathway itself through other mutated genes, such as MDM2 and MDM4. Concerning epigenetic changes in retinoblastoma, RB1 holds a considerable role in controlling numerous oncogenes and tumor suppressor genes, like SYK (spleen tyrosine kinase) gene[13,17].

Except for the RB1 mutations, amplification of another oncogene, MYCN, may lead to retinoblastoma. As such, elevated levels of MYCN have been observed in 3% of all retinoblastoma cases while 1% shows only MYCN amplification without RB1 mutations[19].

Retinoblastoma relies amongst the phenotypic expressions of 13q deletion syndrome, providing that the deleting area includes the 13q14 locus. Symptomatology is characterized by heterogeneity, varying from growth deficiency and mental retardation to microcephaly and other clinical features[20].

Clinical features

The clinical presentation of retinoblastoma is related to the location and growth of the tumor. Leukocoria (white pupil) (Figure 1) is the most typical finding. Nowadays, it is usually recognized by parents as an absent red reflex on digital flash photography. Following leukocoria, strabismus (misaligned eyes) is the second most common clinical feature, when central vision impairment is present. In some cases buphthalmos, pain, vitreous hemorrhage, sterile orbital cellulitis (inflammation caused by necrosis), heterochromia and hypopyon are also observed[21]. Symptomatology shows variation at certain countries such as Soudan[22] and Mali[23]. Lack of awareness along with insufficient access to health resources often leads to delayed diagnosis. In such instances, proptosis, the forward protrusion of the globe, becomes the prevailing clinical feature[24]. Another possible finding is phthisis bulbi which may be the result of retinal detachment, caused by tumors of considerable size[25].

Figure 1: Case of bilateral leukocoria caused by bilateral retinoblastoma.

Based on its growth pattern retinoblastoma is characterized as exophytic or endophytic (Figure 2). Exophytic RB emerges from the outer retina and is correlated to subretinal seeds while endophytic RB is located at the inner retina with a tendency for vitreous seeding. Both of these patterns may also be present simultaneously[26].

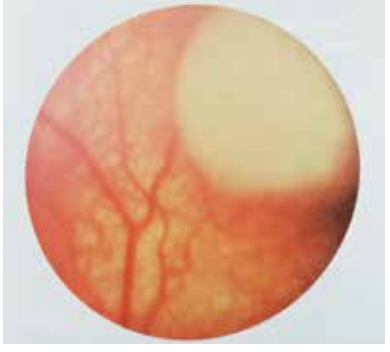

Figure 2: Endophytic form of retinoblastoma.

Diffuse infiltrating retinoblastoma, a variation of RB, accounts for up to 2% of the cases. Its main characteristic is a flat retinal lesion while infiltration of the vitreous and the anterior chamber might be observed, too. Symptomatology differentiates from that of regular retinoblastoma. The primary manifestations are reduced vision, redness and pain, hence masquerading as intraocular inflammation[27]. Vitreous cells followed by pseudohypopyon and increased intraocular pressure are also regular clinical signs. Patients with diffuse infiltrating retinoblastoma are usually older compared to those with typical retinoblastoma[26].

Diagnosis

Clinical features and examination set the diagnosis for retinoblastoma[28]. More accurate RB surveillance is usually performed with examination under anesthesia (EUA)[29]. Adequate diagnosis may be set with indirect ophthalmoscopy after the dilation of the pupil through the administration of a pharmacological agent[6].

Despite the fact that RB is a malignancy, no biopsy is conducted since there is a high risk of tumor spreading along the needle's route[30].

Ocular ultrasonography can identify 92-95% of calcifications, measure the dimensions of the tumor and determine endophytic and exophytic expansion[31].

CT scan is not recommended since exposure to radiation elevates the probability of second primary tumor formation in hereditary retinoblastomas[32].

MRI is used for corroborating the malignancy and mapping its borders[29]. Before enucleation pathological characteristics, such as expansion to the optic nerve (Figure 3) and the choroid coat[33], can be assessed with MRI[31]. Findings of subvitreus seeding and anterior chamber disease[34], as well as calcifications are visible through high-field MRI scanning[33]. It is also crucial for the detection of invisible tumors and trilateral retinoblastoma. In the last case, MRI is applied intraoperatively[35].

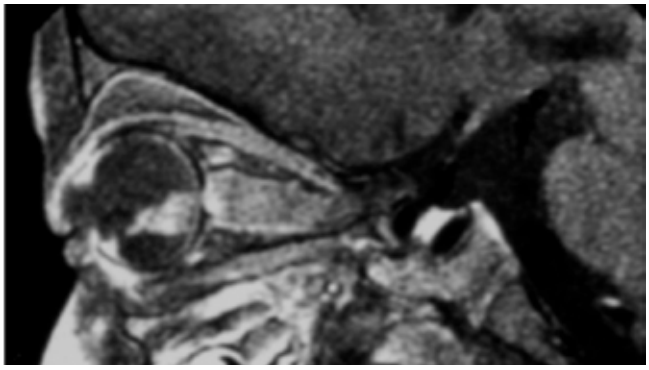

Figure 3: MRI (sagittal enhanced T1-weighted sequence) of retinoblastoma with optic nerve expansion.

Optical Coherence Tomography (OCT) has lately been useful in discerning and monitoring small tumors. It can also evaluate tumor's response to therapy along with possible relapse and visual impairment[36].

Wide-angle photography with digital retinal cameras is valuable for assessing the therapeutic result in addition to RB imaging and monitoring. Fluorescent angiography can be performed with the same system allowing illustration of the tumor's vascular structures, particularly in cases where diagnosis is indefinite[29].

Ultrasound Biomicroscopy (UBM) is utilized for the evaluation of probable anterior segment expansion of retinoblastoma and invasion of the cilliary body[37].

Differential diagnosis includes Coat's disease, persistent hyperplastic primary vitreous (PHPV), toxocara endophthalmitis, medulloepithelioma, uveal melanoma, vitreous hemorrhage, coloboma, rhegmatogenous retinal detachment and retinoma[38,39].

Maternal ultrasound and fetal MRI are proposed for prenatal RB detection from 34th to 38th week of gestation in cases with recognized hereditary RB or germline RB1 mutation. Some centers in order to avoid possible visual impairment by invisible tumors to the above imaging modalities advocate early-term delivery. As far as carriers of RB1 mutation is concerned, postnatal screening for retinoblastoma requires ocular exam within 1-2 weeks of birth performed without anesthesia followed by exams every 2-4 weeks until the infant is 3 months old. Exams under anesthesia are recommended from the 3rd month up to the 5th year of age. As individuals with RB1 mutation have high risk of second primary tumors further examination may be necessary until the age of 18[40].

Classification

The development of a therapeutic plan requires a staging system for retinoblastoma based on its international recognized clinical features. Several classifications have been introduced over time, taking into account the evolvement of treatment options[41].

The first system was developed by Reese and Ellsworth (RE) in 1960s. Its main premise was the prognosis of intraocular disease regarding the first line treatment of the era, external beam radiation (EBRT). Thus, the eyes were categorized into 5 groups (from I-V) based on the favorability of sight maintenance (Table 1)[42]. In the 1990s, intravenous chemotherapy replaced EBRT as the primary conservative treatment. This led to the creation of the International Intraocular Retinoblastoma Classification (IIRC), which follows similar division labeled from A to E[43]. A modifying scheme of IIRC, Intraocular Classification of Retinoblastoma (ICRB) (Table 2), was introduced in 2006 being the current golden standard[44]. Two variations exist; the Philadelphia

I: Very favorable for maintenance of sight	II: Favorable for maintenance of sight	III: Doubtful for maintenance of sight	IV: Unfavorable for maintenance of sight	V: Very unfavorable for maintenance of sight
a) Solid tumor, less than 4 disc diameters,at or behind the equator b) Multiple tumors, less than 4 disc diameters,all at or behind the equator	a) Solid tumor, 4-10 disc diameters,at or behind the equator b) Multiple tumors, 4-10 disc diameters,all at or behind the equator	a) Any lesion anterior to the equator b) Solid tumor, more than 10 disc diameters behind equator	a) Multiple tumors, some more than 10 disc diameters b) Any extension anteriorly to the ora serrata	a) Massive tumors involving more than half of the retina b) Vitreous seeding

Table 1: Reese-Ellsworth Classification

A: Very low risk	B: Low risk	C: Moderate risk	D: High risk	E: Very high risk
Small intraretinal tumors (< 3mm) away from foveola and disc	Tumors > 3mm, macular or juxtapapillary location, or with subretinal fluid	Tumor with focal subretinal or vitreous seeding within 3mm of the tumor,both subretinal and vitreous seeds within 3mm of the tumor	Tumor with diffuse subretinal or vitreous seeding > 3mm from tumor,both subretinal and vitreous seeds >3mm from tumor	Extensive retinoblastoma occupying >50% of the globe with or without neovascular glaucoma,opaque media from hemorrhage in anterior chamber,vitreous or subretinal space,invasion of the postlaminal optic nerve,choroid(>2mm),sclera,orbit,anterior chamber

(ICRB)

Table 2: International Classification of Retinoblastoma

Classification and the Children's Hospital Los Angeles Classification (CHLA)[41].

Regarding extraocular RB, the International Retinoblastoma Staging System (IRSS) was proposed, ranging from conservative treatment (stage 0) to metastatic disease (stage IV) (Table 3)[43].

The most recent edition of the TNM staging (TNM8) combines pathological and clinical aspects with the location of the tumor (intraocular or extraocular)[26]. Heritability is also included contributing to a more precise prognosis[41].

0	I	II	III	IV
Patients treated conservatively	Eye enucleated, completely resected histologically	Eye enucleated, microscopic residual tumor	Regional extension a. Overt orbital disease b. Preauricular or cervical lymph node extension	Metastatic disease a. Hematogenous metastasis (without CNS involvement) 1. Single lesion 2. Multiple lesions b. CNS extension (with or without any other site of regional or metastatic disease) 1. Prechiasmatic lesion 2. CNS mass 3. Leptomeningeal and CSF disease

Table 3: International Retinoblastoma Staging System (IRSS)

Surgical Removal	Radiotherapy	Chemotherapy	Focal therapy
Enucleation	External Beam Radiotherapy (EBRT)	Intravenous chemotherapy (IVC)	Transpupillary thermotherapy (TTT)
	Proton Beam Therapy (PBT)	Intra-arterial chemotherapy (IAC)	Cryotherapy
		Intravitreal chemotherapy (IVitC)	Laser Therapy (Photocoagulation)
		Periocular chemotherapy (POC)	Plaque brachytherapy

Table 4: Treatment options in RB

Therapy

Recent developments in therapy have supplemented traditional methods offering a plethora of treatment options (Table 4)[45].

Enucleation

Enucleation is the primary form of treatment for unilateral group E and advanced cases of group D eyes, particularly if there is a poor prospect of preserving the vision (Table 2)[46]. Clinical findings such as tumors larger than 15mm, orbital inflammation, retinal detachment, neovascularization of the iris, secondary glaucoma, orbital cellulitis and optic nerve expansion are also indications for surgery due to their high histopathological risks[5,45,47,48]. In bilateral cases when the lesions are asymmetrical, enucleation is proposed for the eye with the worst prognostic potential[49]. When conservative treatments are proven unsuccessful, enucleation is the method of choice[50]. Excision of the tumor provides the potential of histopathological examination, hence assessing possible extraocular spread[49]. For cosmetic reasons a prosthetic implant is placed in the eye socket to fill the orbital volume[51].

Radiotherapy

While in the 1980s, external beam radiotherapy (EBRT) was considered the first-line treatment of retinoblastoma, the high risk of developing secondary tumors led to its replacement by other methods[52]. Specifically, the risk for secondary malignancies (e.g. sarcoma) was found to be around 51% at 50 years of age[53]. Currently EBRT is useful for preserving the remaining eye when other treatments are found insufficient, particularly in the cases of diffuse vitreous and subretinal seeding[54]. Other indications of EBRT include intracranial disease, tumors invading the sclera or the orbit[55] and those threatening the macula or the optic nerve along with multifocal RB[56].

The latest update in radiation therapy is proton radiation therapy (PBT). By using a more focused beam the exposure of bones and surrounding soft tissues is minimized, thus reducing the risk of secondary cancers. PBRT is commonly used either in combination with chemotherapy or on its own as an eye salvage technique, when other modalities are proven unsuccessful[56].

Chemotherapy

Since 1990s[57], intravenous chemotherapy (IVC) is used as first line treatment of retinoblastoma or combined with other methods. It usually involves co-administration of 2-, 3- or 4- chemotherapeutic agents with the most common regimen being carboplatin, etoposide and vincristine (CEV)[58]. IVC as monotherapy is reported with success rates of 100% for eyes of group A, 93% of group B and 90% of group C. However, it is less sufficient in controlling the more advanced tumors of group D (47%) and group E (33%). For a more effective approach of group B, C and D tumors, focal therapies follow systemic chemotherapy, since this way the blood-retina barrier becomes more permeable to chemotherapeutics[29]. IVC has also shown efficiency in bilateral cases of intraocular RB management minimizing the possibility of metastasis, pineoblastoma and long-term second malignancies. Systemic chemotherapy has scarce adverse effects, such as neurotoxicity, hyponatremia, nephrotoxicity, ototoxicity, immunosuppression and secondary leukemia[45].

Intra-arterial chemotherapy (IAC) was originally developed in Japan and allows eclectic administration of chemotherapeutics to the eye along with reduced systemic exposure[59]. Infusion of the agent (melphalan, topotecan, carboplatin)6 in the ophthalmic artery is achieved through catheterization of the femoral artery[59]. Melphalan is extensively used alone on the grounds of its high efficacy and short half-life or in combination with topotecan in cases of substantial vitreous seeding[60]. IAC has been recommended for

treatment of unilateral or non-hereditary retinoblastoma[60,61]. Simultaneous treatment of both eyes in bilateral retinoblastoma, called tandem therapy, has also been described[62]. Other applications of IAC include relapsed subretinal seeds and relapsed tumors when IVC and plaque radiotherapy have failed[45]. Among the side effects of IAC that have been reported are retinal detachment (19.3%), vitreous hemorrhage (18.1%), periorbital edema or inflammation (34%) and nausea or vomiting (33.7%)[63].

Intra-arterial and intravenous chemotherapy are often inadequate for the management of vitreous seeds, usually observed in C, D and E groups, due to their distant location from retinal vasculature. Thus, intravitreal chemotherapy (IVitC) was introduced for treating relapsed or refractory vitreous seeds in conjunction with other treatments for addressing the main tumor mass[64]. The most common chemotherapeutic in IVitC is melphalan, too, injected via pars plana[45]. Other drugs include carboplatin, topotecan and methotrexate[65]. Safety measures (e.g. cryotherapy at the injection site) are implemented to avoid possible disperse of the tumor's seeds along the needle's course[66]. Retinal pigment mottling at the location with the highest concentration of the agent, the most frequent side effect, was estimated between 18-43%[65].

Periocular chemotherapy (POC) involves the subconjunctival or subtenon injection of therapeutic agents (carboplatin, topotecan). It is indicated for the treatment of eyes classified in groups D or E with diffuse vitreous seeds that demand higher local dose of chemotherapy. Subtenon injections of carboplatin may be utilized to improve tumor control, specifically if combined with intravenous chemoreduction[45]. In addition to that, subconjuctival chemotherapy also complements laser therapy[29]. Optic nerve ischaemic necrosis and atrophy, reduced ocular motility due to fibrosis and pseudo-preseptal cellulitis are some of the side effects that have been described[67–69].

Focal therapy

Focal therapies include transpupillary thermotherapy, cryotherapy, laser therapy and plaque brachytherapy[26]. These treatments are indicated for group A eyes and following intravenous or intra-arterial chemotherapy in cases of group B, C and D eyes[21].

Transpupillary thermotherapy (TTT) utilizes infrared radiation (810-nm diode laser) to heat the tumor up to 42°C-60°C, avoiding this way coagulation of retinal vessels. TTT is used for local management and tumors positioned posterior to the equator of the globe with dimensions smaller than 4.5mm base and 2.5mm thickness[70].

In transscleralcryotherapy, which is performed under visualization[26], a nitrous oxide cryoprobe freezes the tumor up to -90°C[70] for treating small lesions occupying the anterior half of the globe[45].

In laser therapy, the tumor's vessels are coagulated at temperatures over 65°C with a 520nm argon laser. Laser photocoagulation is used for small posterior malignancies, usually after intravenous chemotherapy, and tumor-related neovascularization of the retina[45].

Plaque brachytherapy is a type of radiation treatment in which a probe with radioisotopes Iodine-125 or Ruthenium-106 is placed on the sclera21 for 5-7 days[29]. Plaque radiotherapy may be used as a primary or, more commonly, as a second-line treatment following failure of previous therapeutic attempts[71].

Conclusion

Parents should be cautious of the visible clinical findings of retinoblastoma, such as leukocoria and strabismus, and immediately seek pediatric consultation. Early diagnosis is in most cases life-saving, preventing extraocular spread of the tumor, and crucial for salvaging both the eye and the vision of the patient. Recently, new therapeutic approaches have emerged allowing for a more targeted treatment while minimizing potential side effects. Current efforts are directed towards alternative chemotherapeutics, molecular and gene therapy, suprachoroidal injections and nanotechnology-based drug-delivery systems[45].

REFERENCES

1. Pizzo P, Poplack D. Principles and Practice of Pediatric Oncology. 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2006.

2. Lochmann D. Retinoblastoma. Adv Exp Med Biol. 2010; 685:220-227.

3. de Jong MC, Kors WA, de Graaf P, Castelijns JA, Kivelä T, Moll AC. Trilateral retinoblastoma: A systematic review and meta-analysis. Lancet Oncol 2014; 15(10):1157-1167.

4. Kivelä T. The epidemiological challenge of the most frequent eye cancer: Retinoblastoma, an issue of birth and death. Br J Ophthalmol 2009; 93(9):1129-1131.

5. Ghassemi F, Khodabande A. Risk definition and management strategies in retinoblastoma: current perspectives. Clin Ophthalmol 2015; 9:985-994.

6. Dimaras H, Corson TW, Cobrinik D, et al. Retinoblastoma. Nat Rev Dis Prim 2015; 1:15-21.

7. Parkin DM, Stiller C, Draper GJ, Bieber C. The international incidence of childhood cancer. Int J Cancer 1988; 42(4):511-520.

8. Knudson AG. Mutation and Cancer: Statistical Study of Retinoblastoma. Proc Natl Acad Sci 1971; 68(4):820-823.

9. Chantada G, Schaiquevich P. Management of Retinoblastoma in Children: Current Status. Pediatr Drugs 2015;

17(3):185-198.

10. Kleinerman RA, Tucker MA, Tarone RE, et al. Risk of new cancers after radiotherapy in long-term survivors of retinoblastoma: An extended follow-up. J Clin Oncol 2005; 23(10):2272-2279.

11. Temming P, Viehmann A, Biewald E, Lohmann DR. Sporadic unilateral retinoblastoma or first sign of bilateral disease? Br J Ophthalmol 2013; 97(4):475-480.

12. Sengupta S, Pan U, Khetan V. Adult onset retinoblastoma. Indian J Ophthalmol 2016; 64(7):485-491.

13. McEvoy JD, Dyer MA. Genetic and Epigenetic Discoveries in Human Retinoblastoma. Crit Rev Oncog 2015; 20(3-4):217-225.

14. Harbour JW. Overview of rb gene mutations in patients with retinoblastoma. Ophthalmol 1998; 105(8):1442-1447.

15. Sage J. The retinoblastoma tumor suppressor and stem cell biology. Genes Dev 2012; 26(13):1409-1420.

16. Dimaras H, Khetan V, Halliday W, et al. Loss of RB1 induces non-proliferative retinoma: Increasing genomic instability correlates with progression to retinoblastoma. Hum Mol Genet 2008; 17(10):1363-1372.

17. Zhang J, Benavente CA, McEvoy J, et al. A novel retinoblastoma therapy from genomic and epigenetic analyses. Nature 2012; 481:329-334.

18. Kooi IE, Mol BM, Massink MPG, et al. A meta-analysis of retinoblastoma copy numbers refines the list of possible driver genes involved in tumor progression. PLoS One 2016; 11(4):e0153323.

19. Thériault BL, Dimaras H, Gallie BL, Corson TW. The genomic landscape of retinoblastoma: A review. Clin Exp Ophthalmol 2014; 42(1):33-52.

20. Ortiz MV, Dunkel IJ. Retinoblastoma. J Child Neurol 2016; 31(2):227-236.

21. Jenkinson H. Retinoblastoma: diagnosis and management—the UK perspective. Arch Dis Child 2015; 100(11):1070-1075.

22. Ali AAE, Elsheikh SMA, Elhaj A, et al. Clinical presentation and outcome of retinoblastoma among children treated at the National Cancer Institute (NCI) in Gezira, Sudan: A single institution experience. Ophthalmic Genet 2011; 32(2):122-125.

23. Boubacar T, Fatou S, Fousseyni T, et al. A 30-month prospective study on the treatment of retinoblastoma in the Gabriel Toure Teaching Hospital, Bamako, Mali. Br J Ophthalmol 2010; 94(4):467-469.

24. Menon BS, Reddy SC, Wan Mazial WM, Ham A, Rosline H. International notes extraocular retinoblastoma. In: Medical and Pediatric Oncology 2000; 35(1):75-76.

25. Kashyap S, Meel R, Pushker N, et al. Phthisis bulbi in retinoblastoma. Clin Exp Ophthalmol 2011;39(2):105-110.

26. Rao R, Honavar SG. Retinoblastoma. Indian J Pediatr 2017; 84(12):937-944.

27. Jijelava KP, Grossniklaus HE. Diffuse anterior retinoblastoma: A review. Saudi J Ophthalmol 2013; 27(3):135-139.

28. Dimaras H, Kimani K, Dimba EA, et al. Retinoblastoma. Lancet 2012; 379(9824):1436-1446.

29. Syed R, Ramasubramanian A. Advances in Management of Retinoblastoma. Adv Ophthalmol Optom 2017; 2(1):87-100.

30. Karcioglu ZA. Fine needle aspiration biopsy (FNAB) for retinoblastoma. Retina 2002; 22(6):707-710.

31. De Graaf P, Göricke S, Rodjan F, et al. Guidelines for imaging retinoblastoma: Imaging principles and MRI standardization. Pediatr Radiol 2012; 42(1):2-14.

32. McCarthy M, Glick R, Green J, et al. Comfort First: An evaluation of a procedural pain management programme for children with cancer. Psychooncology 2013; 22(4):775-782.

33. Razek AAKA, Elkhamary S. MRI of retinoblastoma. Br J Radiol 2011; 84(1005):775-784.

34. Galluzzi P, de Jong MC, Sirin S, et al. MRI-based assessment of the pineal gland in a large population of children aged 0–5 years and comparison with pineoblastoma: part I, the solid gland. Neuroradiology 2016; 109(3): 535-544.

35. Hlavac M, Wirtz CR, Halatsch M-E. Intraoperative magnetic resonance imaging. HNO 2017; 65(1):25-29.

36. Berry JL, Cobrinik D, Kim JW. Detection and Intraretinal Localization of an “Invisible” Retinoblastoma Using Optical Coherence Tomography. Ocul Oncol Pathol 2016; 2(3):148-152.

37. Moulin AP, Gaillard MC, Balmer A, Munier FL. Ultrasound biomicroscopy evaluation of anterior extension in retinoblastoma: A clinicopathological study. Br J Ophthalmol 2012; 96(3):337-340.

38. Shields CL, Schoenberg E, Kocher K, Shukla SY, Kaliki S, Shields JA. Lesions simulating retinoblastoma (Pseudoretinoblastoma) in 604 cases: Results based on age at presentation. Ophthalmology 2013; 120(2):311-316.

39. Grossniklaus HE. Retinoblastoma. Fifty years of progress. the LXXI Edward Jackson memorial lecture. Am J Ophthalmol 2014; 158(5):875-891.

40. Kamihara J, Bourdeaut F, Foulkes WD, et al. Retinoblastoma and Neuroblastoma predisposition and surveillance. Clin Cancer Res 2017; 23(13):e98-e106.

41. Maitray A, Khetan V. Classification of retinoblastoma: Evolution with time and the need for uniformity. Oman J Ophthalmol 2017; 10(3):133.

42. Reese AB, Ellsworth RM. The evaluation and current concept of retinoblastoma therapy. Trans Am Acad Ophthalmol Otolaryngol 1963; 67:164-172.

43. Chantada G, Doz F, Antoneli CBG, et al. A proposal for an international retinoblastoma staging system. Pediatr Blood Cancer 2006; 47(6):801-805.

44. Murphree AL. Intraocular retinoblastoma: The case for a new group classification. Ophthalmol Clin North Am

2005; 18(1):41-53.

45. Mendoza PR, Grossniklaus HE. Therapeutic options for retinoblastoma. Cancer Control 2016; 23(2):99-109.

46. Kim JW, Murphree AL, Singh AD. Retinoblastoma: Treatment Options. In: Clinical Ophthalmic Oncology. Berlin, Heidelberg: Springer Berlin Heidelberg; 2015:89-107.

47. Meel R, Radhakrishnan V, Bakhshi S. Current therapy and recent advances in the management of retinoblastoma. Indian J Med Paediatr Oncol 2012; 33(2):80-88.

48. Epelman S. Preserving Vision in Retinoblastoma Through Early Detection and Intervention. Curr Oncol Rep 2012; 14(2):213-219.

49. Appukuttan B, Biswas J, Khetan V. Enucleation in retinoblastoma: Pros and cons. Expert Rev Ophthalmol. 2013; 8(4)351-353.

50. Ray A, Gombos DS. Retinoblastoma: An Overview. Indian J Pediatr 2012; 79(7):916-921.

51. Shields JA, Shields CL, De Potter P. Enucleation technique for children with retinoblastoma. J Pediatr Ophthalmol Strabismus 1992; 29(4):213-215.

52. Shields CL, Fulco EM, Arias JD, et al. Retinoblastoma frontiers with intravenous, intra-arterial, periocular, and intravitreal chemotherapy. In: Eye (Basingstoke) 2013; 27(2):253-264.

53. Friedman DN, Chou JF, Oeffinger KC, et al. Chronic medical conditions in adult survivors of retinoblastoma: Results of the Retinoblastoma Survivor Study. Cancer 2016; 122(5):773-781.

54. Abramson DH, Beaverson KL, Chang ST, Dunkel IJ, McCormick B. Outcome following initial external beam radiotherapy in patients with Reese-Ellsworth group Vb retinoblastoma. Arch Ophthalmol 2004; 122(9):1316-1323.

55. Rodriguez-Galindo C, Chantada GL, Haik BG, Wilson MW. Treatment of retinoblastoma: current status and future perspectives. Curr Treat Options Neurol 2007; 9(4):294-307.

56. Kim J-Y, Park Y. Treatment of Retinoblastoma: The Role of External Beam Radiotherapy. Yonsei Med J 2015; 56(6):1478.

57. Kingston JE, Hungerford JL, Madreperla SA, Plowman PN. Results of combined chemotherapy and radiotherapy for advanced intraocular retinoblastoma. Arch Ophthalmol (Chicago, Ill 1960) 1996; 114(11):1339-1343.

58. Shields CL, Lally SE, Leahey AM, et al. Targeted retinoblastoma management: When to use intravenous, intra-arterial, periocular, and intravitreal chemotherapy. Curr Opin Ophthalmol 2014; 27(2): 253-264.

59. Gobin YP, Dunkel IJ, Marr BP, Brodie SE, Abramson DH. Intra-arterial chemotherapy for the management of retinoblastoma four-year experience. Arch Ophthalmol 2011; 129(6):732-737.

60. Zanaty M, Barros G, Chalouhi N, et al. Update on intra-arterial chemotherapy for retinoblastoma. Sci World J 2014; DOI:10.1155/2014/869604.

61. Shields CL, Jorge R, Say EAT, et al. Unilateral retinoblastoma managed with intravenous chemotherapy versus intra-arterial chemotherapy. Outcomes based on the international classification of retinoblastoma. Asia-Pacific J Ophthalmol 2016; 5(2):97-103.

62. Abramson DH, Marr BP, Francis JH, et al. Simultaneous bilateral ophthalmic artery chemosurgery for bilateral retinoblastoma (tandem therapy). PLoS One 2016; 11(6):e0156806.

63. Yousef YA, Soliman SE, Astudillo PPP, et al. Intra-arterial chemotherapy for retinoblastoma: A systematic review. JAMA Ophthalmol 2016; 134(5):584-591.

64. Chung CY, Medina CA, Aziz HA, Singh AD. Retinoblastoma: Evidence for stage-based chemotherapy. Int Ophthalmol Clin 2015; 55(1):63-75.

65. Shields C, Manjandavida F. The role of intravitreal chemotherapy for retinoblastoma. Indian J Ophthalmol 2015; 63(2):141-145.

66. Munier FL, Gaillard MC, Balmer A, Beck-Popovic M. Intravitreal chemotherapy for vitreous seeding in retinoblastoma: Recent advances and perspectives. Saudi J Ophthalmol 2013; 27(3):147-150.

67. Mulvihill A, Budning A, Jay V, et al. Ocular motility changes after subtenon carboplatin chemotherapy for retinoblastoma. Arch Ophthalmol 2003; 121(8):1120-1124.

68. Schmack I, Hubbard GB, Kang SJ, Aaberg TM, Grossniklaus HE. Ischemic Necrosis and Atrophy of the Optic Nerve After Periocular Carboplatin Injection for Intraocular Retinoblastoma. Am J Ophthalmol 2006; 142(2):310-315.

69. Kiratli H, Kocabeyoğlu S, Bilgiç S. Severe pseudo-preseptal cellulitis following sub-Tenon's carboplatin injection for intraocular retinoblastoma. J AAPOS 2007; 11(4):404-405.

70. Chawla B, Jain A, Azad R. Conservative treatment modalities in retinoblastoma. Indian J Ophthalmol 2013; 61(9):479-485.

71. Simpson ER, Gallie B, Laperrierre N, et al. The American Brachytherapy Society consensus guidelines for plaque brachytherapy of uveal melanoma and retinoblastoma. Brachytherapy 2014; 13(1):1-14.