Symposium

Recent advances and challenges in the management of retinoblastoma

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The treatment of retinoblastoma (Rb) has improved significantly in recent times. Worldwide, there is an increasing trend to use conservative treatment modalities that aim to preserve the globe as well as vision with minimum morbidity. Recently, the use of targeted delivery of chemotherapy to the eye in the form of selective intra-arterial and intravitreal chemotherapy has shown promising results. Radiotherapy is beneficial in selected cases, either in the form of plaque brachytherapy or as external beam radiotherapy. Orbital disease carries a poor prognosis for survival. However, a multimodal treatment protocol has improved survival in children with extraocular disease. Nevertheless, challenges remain, especially for the developing world. This review aims to highlight recent advances in the management of Rb that have contributed towards improving treatment outcomes and also discuss the challenges ahead, with special reference to the Indian scenario.

Key words: Challenges, recent advances, retinoblastoma

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Retinoblastoma (Rb) is the most common intraocular malignancy of childhood. The incidence is reported to be approximately 1 in 18,000 live births worldwide.[1,2] Leukocoria is the most frequent symptom at presentation, and other symptoms include poor vision, redness, squint, or proptosis.[2] The majority of children are diagnosed before 5 years of age. The disease may be unilateral or bilateral; bilateral involvement is seen in one-third of cases. Although potentially curable, the prognosis for survival is dependent on early diagnosis and appropriate therapy. The management of Rb is complex and challenging and often requires a multidisciplinary approach. Goals of therapy consist of life salvage, globe salvage, and vision preservation, whenever possible.

Fortunately, treatment of Rb has improved significantly over recent years. In the initial stages of the disease, the aim is to preserve the globe as well as vision, with minimum morbidity. This has been made possible with the successful use of intravenous chemotherapy and focal treatment. Recently, the use of targeted delivery of chemotherapy to the eye in the form of selective intra-arterial and intravitreal chemotherapy has shown promising results. Radiotherapy is beneficial in selected cases, either in the form of plaque brachytherapy or as external beam radiotherapy (EBRT). For advanced orbital disease, a presentation not uncommon in developing countries, a multimodal treatment protocol has improved survival. Nevertheless, challenges remain, especially for the developing world. This review aims to highlight recent advances in the management of Rb that have contributed towards improving treatment outcomes and to discuss the challenges ahead, with special reference to the Indian scenario.

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Classification and Staging of Retinoblastoma

The Reese and Ellsworth classification was developed in the 1960s to predict globe salvage after EBRT.[3] However, with the increasing popularity of systemic chemotherapy, the need for a new classification system arose. The International Classification of Rb was therefore developed, and it was universally accepted as a good predictor of chemoreduction success.[4,5] Recently, the American Joint Committee on Cancer has formulated the 8th edition of Rb staging, with the view that it will be universally accepted to define the extent of disease at diagnosis and to predict eye survival, metastatic risk, and patient survival. Unique to the 8th edition tumor node metastasis (TNM) staging for Rb, is the inclusion of germ line cancer predisposition, which incurs a high risk for new postdiagnosis Rb tumors and second primary tumors such as osteosarcoma and cutaneous melanoma, thus affecting overall patient survival. It has introduced the stage category H to indicate the germ line status of RB1 gene (H1) inferred clinically by bilateral Rb, Rb with an intracranial primitive neuroectodermal tumor (i.e., trilateral Rb), patient with family history of Rb, or molecular definition of a constitutional RB1 gene mutation.[6]

Globe-saving Treatments

While enucleation remains the standard of care for advanced intraocular tumors, conservative treatment which can result in globe salvage and preservation of useful vision is being

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successfully used for less advanced disease (Groups A-D, International Classification System).[7] These therapies include systemic chemotherapy, focal consolidation with transpupillary thermotherapy, laser photocoagulation and cryotherapy, radiation treatment with plaque brachytherapy or EBRT, and local injections of chemotherapeutic agents through the subtenon or subconjunctival route, as an adjunct to systemic chemotherapy. The most common chemotherapy drugs used intravenously are vincristine, etoposide, and carboplatin (VEC). Systemic chemotherapy combined with focal therapy has been the mainstay of globe-preserving treatment for less advanced disease.[8] In a recent study published from our center, systemic chemotherapy and focal consolidation was found to achieve effective tumor control in early-stage Rb, with outcomes that were comparable to those reported from the West.[8]

Selective intra-arterial chemotherapy

Although systemic chemotherapy in combination with focal therapy has achieved good outcomes, intravenous chemotherapy can lead to serious toxic side effects including myelosuppression and infection. As a result, newer treatment approaches have focused on localized delivery of chemotherapy to minimize the systemic side effects of intravenous chemotherapy. One such novel approach is selective intra-arterial chemotherapy (SIAC), which delivers targeted chemotherapy to the eye harboring the tumor through the ophthalmic artery.[9] Being a site-directed approach, it has fewer systemic side effects as compared to intravenous chemotherapy. Melphalan is the drug of choice for intra-arterial chemotherapy. In 2004, the Japanese investigators described the technique of "selective ophthalmic artery infusion" (SOAI), where a microballoon catheter was positioned by a transfemoral artery approach at the cervical segment of the internal carotid artery just distal to the orifice of the ophthalmic artery.[10,11] The Japanese technique of SOAI was further developed into direct intra-arterial (ophthalmic artery) infusion under the pioneering work of Abramson and Gobin in New York.[9] They introduced the technique of super-selective infusion by advancing a microcatheter into the orifice of the ophthalmic artery by a transfemoral artery approach. In a Phase I/II clinical trial, Abramson *et al*. reported their initial experience with intra-arterial ophthalmic artery chemotherapy using melphalan in ten children with advanced Rb who were indicated for enucleation.[9] They reported a dramatic regression of tumors, vitreous seeds, and subretinal seeds (SRS) in each case.[9] No severe systemic side effects such as sepsis, anemia, neutropenia, or death occurred.[12] In another study, Gobin *et al*. reported their experience of selective ophthalmic artery cannulation on 95 eyes of 78 patients with unilateral or bilateral advanced intraocular Rb.[12] The Kaplan–Meier estimates of ocular event-free survival rates at 2 years were 70.0% for all eyes, 81.7% for eyes that received IAC as primary treatment, and 58.4% for eyes that had previous treatment failure with intravenous chemotherapy and/or external beam radiation therapy.[12] There were no permanent extraocular complications, thus suggesting that IAC is safe and effective for the treatment of advanced intraocular Rb.[12] Since then, several investigators have reported their experience with IAC.[13-30] In a study done by Tuncer *et al*., 26 Group D eyes of 24 treatment-naïve Rb patients managed primarily with IAC were included.[19] Each eye received a mean of three IAC sessions/eye (range, 2–5 sessions). Complete regression of the main tumor was achieved in 23 of 24 eyes. One eye with partial regression required enucleation due to ciliary body involvement by the tumor. They concluded that enucleation or external beam radiotherapy could be avoided in the majority of eyes with advanced intraocular Rb managed primarily with IAC.[19] In another study, Michaels *et al*. reported the toxicities and outcome of 19 eyes in 17 patients with Rb receiving selective ophthalmic artery infusion chemotherapy (SOAIC) treatment between 2008 and 2013.[20] From the 87 treatments, mild local reactions were common. Myelosuppression was more common after triple-agent SOAIC than single-agent melphalan. Ocular salvage was achieved in 11 of 19 eyes and associated with triple-agent therapy.[20] Simultaneous bilateral ophthalmic artery chemosurgery (OAC) for bilateral Rb (tandem therapy) has also been reported, wherein 116 eyes were salvaged.[21] Kaplan–Meier ocular survival was 99.2% at 1 year, 96.9% at 2 and 3 years, and 94.9% for years 4 through 7.[21] There were no cases of metastatic disease or metastatic deaths with a mean follow-up of 3.01 years.[21]

The effect of IAC as a rescue therapy was investigated in recurrence of Rb in eyes previously treated with IAC, using melphalan (5 mg, 7.5 mg) alone or with additional topotecan (1 mg).[22] The study concluded that rescue IAC provided tumor control in 75% of cases and globe salvage in 67%.[22] Rescue IAC could be considered in children who fail initial IAC, especially if the opposite eye had been enucleated.[22] Chen M *et al*. have studied the effect of IAC in infants <3 months.[23] The mean patient age at the first IAC treatment was 10.4 weeks (range 4.9–12.9 weeks). A total of 28 catheterizations were performed. After a mean follow-up of 28.3 months (range 9–65 months), tumor regression was observed in 12 of 13 eyes.[23] All patients were alive and no patient developed metastatic disease or other malignancies. Their study suggests that IAC as primary therapy is a feasible and promising treatment for Rb in infants <3 months of age.[23] An interesting case of IAC in adult onset Rb has been described.[24] A 32-year-old man with active unilateral Group D Rb that was recurrent following EBRT was treated with IAC, leading to tumor regression. Additional plaque radiotherapy and intravitreal chemotherapy were required for complete control.[24] In a retrospective case series, Shields *et al*. compared the effects of IAC before and after intravitreal chemotherapy.[25] Sixty-six eyes of 66 patients with untreated unilateral Rb were studied. IAC into the ophthalmic artery under fluoroscopic guidance was performed using melphalan in every case, with additional topotecan as necessary. They found that using IAC plus additional intravitreal chemotherapy (as needed for vitreous seeding) improved globe salvage in eyes with advanced Rb.[25] Leal-Leal *et al*. have reported their experience of globe salvage with intra-arterial topotecan-melphalan chemotherapy in children with a single eye.[26] All patients were treated with three courses of a combination of melphalan 4 mg and topotecan 1 mg. They concluded that SIAC is safe and effective for preventing enucleation of 55% of affected eyes in this group of patients.[26] In another interesting study, the results of IAC for control of persistent or recurrent sub-retinal seeds following previous chemotherapy for Rb were reported.[27] A total of thirty eyes of 29 patients were included in this study. Each eye received a mean of three IAC sessions. The authors concluded that IAC can be an effective second- or third-line therapy in the management of massive persistent or recurrent sub-retinal seeds from Rb following previous chemotherapy.[27]

IAC for Rb is not always a straightforward procedure, and it may require an adaptable approach. A study done by Bertelli *et al*. illustrates strategies used when the ophthalmic artery is difficult to catheterize or not visible, and it ascertains the effectiveness and safety of these strategies.[28] They recognized three different patterns of drug delivery: a fixed pattern through the ophthalmic artery, a fixed pattern through branches of the external carotid artery, and a variable pattern through either the ophthalmic or the external carotid artery. Alternative routes of IAC for intraocular Rb appeared in the short term as effective and safe as the traditional drug infusion through the ophthalmic artery.[28] Yannuzzi *et al*. compared enucleation and OAC and found that there were more orbital recurrences in the group primarily treated with enucleation. OAC for advanced intraocular Rb was not found to increase the chance of orbital recurrence, metastatic disease, or death compared with primary enucleation in their study.[29] Recently, a study[30] has described the outcomes and complications of selective IAC in Rb in Indian eyes. It was a retrospective interventional case series, in which 6 eyes with Rb underwent IAC using melphalan (3 mg/5 mg/7.5 mg) and topotecan (1 mg) (n = 4) or melphalan (3 mg/5 mg/7.5 mg) alone (n = 2). A mean of three IAC sessions were given in each eye. Following IAC, three cases (50%) showed complete regression of the main tumor, 2 (33%) had partial regression, while 1 case (17%) showed no response. Diffuse choroidal atrophy and vitreous hemorrhage were observed in 1 (17%) eye each. There was no hematologic toxicity or cerebrovascular events. It was concluded that IAC could be considered to be an effective therapy for globe preservation though larger studies with longer follow-up are required for adequately validating the results.[30]

Intravitreal chemotherapy

Vitreous seeds remain the biggest challenge in the management of Rb as they have a poor response to intravenous chemotherapy. Intravenous chemotherapy has poor penetration in the avascular vitreous cavity. Intravitreal chemotherapy is not a primary treatment modality but used as a salvage therapy in cases of recalcitrant and recurrent vitreous seeds.[31] Melphalan is a cytotoxic nitrogen mustard derivative alkylating agent that inhibits both DNA and RNA synthesis. The use of intravitreal melphalan is based on *in vitro* studies conducted by Inomata and Kaneko. Among the 12 anticancer drugs that were studied, they found melphalan to be the most effective against Rb.[32] Munier *et al*.[33] have used melphalan as the drug of choice in a dose of 20–30 μg/0.1 ml. The injection is given 3–3.5 mm away from limbus. The globe is rotated after injection for the uniform distribution of drug. After taking out the needle, triple freeze-thaw cryotherapy application is done on the needle track to avoid needle-track seeding. The injection can be repeated every 7–10 days until complete response is achieved. They have also described the types of regression of vitreous seeding: (1) complete disappearance (regression type 0); (2) refringent and/or calcified residues (regression type I); (3) amorphous, nonspherical, inactive residues (regression type II); or (4) a combination of the last two (regression type III).[33] The followings are the contraindications for intravitreal injection: Anterior segment/ciliary body invasion/other features of Group E Rb, the presence of complete PVD, diffuse vitreous seeds in all quadrant, and total retinal detachment.[33] Munier *et al*.[33] reported a vitreous seed regression rate of 87% in eyes that had already been previously treated with systemic intravenous and/or IAC. Shields *et al*. have shown a 100% success rate of intravitreal chemotherapy at 2-year follow-up.[34] Some authors have also used topotecan as intravitreal injection. Topotecan has a longer half-life; it is used in a concentration of 8–20 μg/0.04 ml. Ghassemi *et al*. studied the effect of intravitreal topotecan (8–20 μg in 0.04 mL of balanced salt solution) combined with melphalan (40 μg in 0.04 mL of diluent) in nine eyes and found the combination to be safe and effective.[35]

The effects of intravitreal chemotherapy on retinal function as studied on electroretinogram (ERG) are conflicting. Brodie *et al*. reported that photopic ERG was not affected following melphalan injection, indicating preservation of retinal function after a dosage of 20–30 μg,[36] whereas Francis *et al*. in their study have reported reduced ERG amplitude, indicating permanent retinal toxicity.[37] The risk of extraocular spread following intravitreal injection in Rb was evaluated by Smith *et al*.[38] Of the 315 eyes of 304 patients who underwent 1300 injections, the proportion of patients with extraocular spread was found to be 0.003.[38]

Radiotherapy

Radiation therapy has an established role in selected patients. It may be in the form of plaque brachytherapy or EBRT. The indications for plaque brachytherapy include solitary tumors that are located anterior to the equator up to the ora serrata and recurrent or residual tumors after primary chemotherapy or failed EBRT.[39-41] Radioisotopes such as iodine (I^{125}) and ruthenium (Ru^{106}) are the most commonly used isotopes. Iodine (I^{125}) seeds are inserted into a gold carrier to protect normal surrounding tissue from radiation. The radiation dose required is calculated by dosimetry planning to provide up to 40 Gy to the tumor apex. The plaque is kept *in situ* until the desired radiation dose has been delivered, usually over a period of 2–4 days. Special plaques with a notch are used to treat tumors adjacent to the optic disc. Side effects of radiation therapy include dryness of eye, irritation, madarosis, cataract, scleral necrosis, radiation retinopathy or papillopathy, optic neuropathy, and strabismus. Second malignancies do not appear to be associated with this type of local therapy. In one study on the role of plaque brachytherapy in Rb, Shields *et al*. reported that plaque radiotherapy provided tumor control in 79% of cases at 5-year follow-up.[39] It was found to be particularly useful for those tumors that failed treatment with other conservative modalities.[39] Tumors in young patients without vitreous or subretinal seeding showed the best long-term control.[39] Plaque brachytherapy has also come up not only as a secondary treatment modality for recurrent or recalcitrant tumor but also as a primary treatment. The American Brachytherapy Society Ophthalmic Oncology Task Force recommends primary brachytherapy for unilateral anterior lesions that are <15 mm in base and up to 10 mm in thickness and without vitreous seeding.[42]

In the prechemotherapy era, EBRT was extensively used for the treatment of Rb. With the advent of systemic chemotherapy, the popularity of EBRT declined because of side effects such as development of secondary malignancies and radiation-induced complications. However, in recent times, there has been substantial advancement in radiation therapy, and the advent of newer radiotherapy techniques has led to greatly improved radiation delivery to the target and more conformal treatment plans with better normal tissue sparing. These include

intensity modulated radiotherapy, stereotactic conformal radiotherapy (SCR), volumetric modulated arc therapy, proton therapy, and helical tomotherapy.[43] SCR is a noninvasive radiotherapy technique that uses highly accurate positioning to deliver treatment with small beams and can provide an alternative to brachytherapy. A recent study has shown that SCR provides more homogeneous dose within the target volume and similar or lower doses to the surrounding normal tissues.[44] However, additional studies with long-term results are needed to prove its efficacy over plaque therapy. Proton beam therapy provides a uniform dose coverage of the target, and unlike photon beams, it has no exit dose and distributes no energy beyond the target. These unique properties reduce the incidence of late effects of radiation.[45] However, proton therapy is expensive and is currently not widely available. The main indications of EBRT are chemoresistant cases of intraocular Rb, as an adjuvant therapy in residual microscopic disease after enucleation surgery, and as part of multimodal therapy for orbital Rb.

Extraocular Retinoblastoma

Although extraocular disease is rare in the developed countries, it is not an unusual feature in the developing world, where extraocular disease constitutes 20%–50% of all Rb cases.[46-48] The management of orbital Rb remains a challenge as orbital involvement is associated with a 10–27 times higher risk of metastasis when compared with cases without orbital extension.[49] In the past, orbital Rb was treated with orbital exenteration, which is a mutilating and disfiguring surgery. Nowadays, the preferred management approach involves a multimodal protocol which consists of neoadjuvant chemotherapy (NAC), enucleation surgery, EBRT, and adjuvant chemotherapy.[50-53] Initially, a combination of high-dose chemotherapeutic agents is used for inducing tumor regression. After enucleation, orbital EBRT and adjuvant chemotherapy are given to eradicate microscopic residual disease and prevent metastasis.

There is paucity of literature on orbital Rb, and treatment strategies are still evolving. Recently, a prospective randomized comparative study on 54 cases of Stage III Rb (International Retinoblastoma Staging System)[54] was published from our center.[55] Treatment consisted of a multimodal protocol with NAC, enucleation, orbital EBRT, and adjuvant chemotherapy. For chemotherapy, patients were randomized into two groups; one group was treated with high-dose triple-drug chemotherapy consisting of VEC and the other group with carboplatin and etoposide, alternating with cyclophosphamide, idarubicin, and vincristine (five drugs). The main outcome measures were survival probability, cause of death, and chemotherapy-related toxicity.[55] The mean follow-up was 21.3 months (standard deviation ± 11.34). The overall Kaplan–Meier survival probability was 80% and 42% at 1 year and 4 years, respectively.[55] The Kaplan–Meier survival probability at 1 year was similar in both groups (81% and 79%). However, at 4 years, the survival probability for VEC-treated cases was higher [63% vs. 25%], with a strong trend of better survival over time (P = 0.05).[55] Central nervous system (CNS) metastasis was the most common cause of relapse and death. Two cases in the five drugs' group died due to sepsis following febrile neutropenia. Grade 3 and Grade 4 hematological toxicities were also more common in children treated with five drugs' therapy, with a significant difference in Grade 4 neutropenia (P = 0.002). No case required orbital exenteration. The results of our study showed more effective tumor control and a better safety profile with the VEC protocol, which was recommended as systemic chemotherapy for nonmetastatic orbital Rb.[55]

Genetics and Prenatal Diagnosis

Rb usually occurs when both alleles of the RB1 tumor suppressor gene get inactivated in a precursor retinal cell, which is followed by mutations in some other specific genes.[56,57] Both alleles may be lost from a retinal cell from which a tumor arises (nonheritable Rb), or it could be a germ line mutation, in which case, there is a predisposition for the development of multiple retinal tumors during childhood and even other cancers later in life.[56] Children with RB1 germ line mutation usually have tumor at birth which is bilateral, mostly on posterior pole affecting the macula.[58,59] Because of such location, even focal treatment like laser will lead to visual compromise. Tumors developing later in life are usually peripheral, thus with a better visual outcome.[58,60] Soliman *et al*.[61] have done a study to compare the conventional postnatal screening of familial Rb with prenatal RB1 mutation identification followed by planned early-term delivery. It was a retrospective observational study comparing two cohorts. Cohort 1 comprised of spontaneously delivered babies examined within 1 week of birth and confirmed to have RB1 mutation postnatally. Cohort 2 comprised of babies prenatally diagnosed by amniocentesis to have RB1 allele and planned for early-term delivery. They concluded that in case of a parent having Rb, prenatal molecular diagnosis with early-term delivery increased the chances of infants having no detectable tumors at birth, better vision outcomes, and less invasive therapy. Therefore, prenatal diagnosis facilitates anticipatory planning for both the child and family.

The Indian Scenario and Challenges Ahead

Studies from different parts of the world have shown a wide variation in the clinical presentation and survival outcomes of children affected by Rb.[62-67] Unlike the West which has excellent survival rates, mortality in developing nations is as high as 40%–70%, mainly due to late presentation.[63] The clinical presentation and survival of children with Rb were recently reported from our center in a large series of 600 cases.[46] Delay in presentation was a matter of concern. Extraocular spread was observed in 28% cases, and metastasis to the CNS was noted at presentation in 15.7% of extraocular cases.[46] These findings reflect a lack of awareness regarding early signs of RB, inadequate health-care facilities at the primary and secondary levels of health care, delay in the referral system, and poor compliance to treatment, a feature common to most developing nations. Within the intraocular group, advanced Group D/E tumors constituted 78% cases.[46] Due to advanced stage at presentation, enucleation was the most commonly recommended treatment. A similar high rate of enucleation has also been reported from China,[68] where the majority of children presented with advanced disease. In our series, less advanced tumors (Group A–C) were picked up less often among unilateral cases as compared to bilateral cases (5.3% vs. 38.4% in unilateral and bilateral groups, respectively). The main reason for picking up early tumors was either during screening of siblings with a positive family history or due

to advanced disease in the fellow eye.[46] Our observation of identifying less advanced disease more often in bilateral Rb was consistent with that reported by Zhao *et al*.[68] in Chinese children. For intraocular disease, globe salvage rates for Group A–Group D disease in our series were 100%, 94%, 83%, and 54%, respectively, which were comparable with those reported by Shields *et al*.[69] (100%, 93%, 90%, and 47%). The mortality rate was 24%, and the cumulative 5-year survival probability was 65%, which is similar to the figure of 64.4% reported from Taiwan.[67] This survival rate is considerably lower than the 5-year survival rate seen in the USA (95%),[70] Japan (93%),[71] and Iran (83%).[66] In our study, extraocular invasion was predictive of low survival (hazard ratio 5.04, $P < 0.001$).[46] Socioeconomic and cultural factors also play a role in influencing treatment decisions. While Rb does not have a sex predilection, our study found a male preponderance which could be due to the lack of attention towards the girl child in our country, especially in rural areas.[46] Another study from India[72] reported on the histopathologic features of 232 enucleated eyes of Rb. The authors found that the incidence of choroidal and optic nerve infiltration was higher in Asian Indian children than among children from the West, and they attributed this to delayed diagnosis or to a difference in the biological behavior of tumors occurring in the Asian Indian population.

Overcoming the Challenges - What can be Done?

Our study on Indian children found that delayed presentation due to lack of awareness and inaccessibility to proper medical facilities at the primary and secondary levels of health care were major obstacles in achieving high cure rates.[46] These hurdles need to be overcome by making efforts toward facilitating early diagnosis and avoiding delays in the referral system.[46] A nationwide awareness campaign to educate the public and health-care professionals about early signs of Rb is required. Strengthening of medical facilities for diagnosing and treating Rb at the primary and secondary levels of health care will also go a long way in reducing mortality and morbidity associated with the disease and lead to improved outcomes that are comparable with the West.[46]

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Conflicts of interest

There are no conflicts of interest.

References

1. Houston SK, Murray TG, Wolfe SQ, Fernandes CE. Current update on retinoblastoma. Int Ophthalmol Clin 2011;51:77-91.
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.
3. Reese AB, Ellsworth RM. The evaluation and current concept of retinoblastoma therapy. Trans Am Acad Ophthalmol Otolaryngol 1963;67:164-72.
4. Linn Murphree A. Intraocular retinoblastoma: The case for a new group classification. Ophthalmol Clin North Am 2005;18:41-53, viii.
5. Shields CL, Shields JA. Basic understanding of current classification and management of retinoblastoma. Curr Opin Ophthalmol 2006;17:228-34.
6. Amin MB, Edge SB, Greene FL, Byrd DR, Brookland RK, Washington MK, *et al.*, (editors). Retinoblastoma.AJCC Cancer Staging Manual. 8th ed., Ch. 68. New York: Springer; 2017. p. 819-31.
7. Chawla B, Jain A, Azad R. Conservative treatment modalities in retinoblastoma. Indian J Ophthalmol 2013;61:479-85.
8. Chawla B, Jain A, Seth R, Azad R, Mohan VK, Pushker N, *et al.* Clinical outcome and regression patterns of retinoblastoma treated with systemic chemoreduction and focal therapy: A prospective study. Indian J Ophthalmol 2016;64:524-9.
9. Abramson DH, Dunkel IJ, Brodie SE, Kim JW, Gobin YP. A phase I/II study of direct intraarterial (ophthalmic artery) chemotherapy with melphalan for intraocular retinoblastoma initial results. Ophthalmology 2008;115:1398-404, 1404.e1.
10. Kaneko A, Suzuki S. Eye-preservation treatment of retinoblastoma with vitreous seeding. Jpn J Clin Oncol 2003;33:601-7.
11. Suzuki S, Kaneko A. Management of intraocular retinoblastoma and ocular prognosis. Int J Clin Oncol 2004;9:1-6.
12. Gobin YP, Dunkel IJ, Marr BP, Brodie SE, Abramson DH. Intra-arterial chemotherapy for the management of retinoblastoma: Four-year experience. Arch Ophthalmol 2011;129:732-7.
13. Peterson EC, Elhammady MS, Quintero-Wolfe S, Murray TG, Aziz-Sultan MA. Selective ophthalmic artery infusion of chemotherapy for advanced intraocular retinoblastoma: Initial experience with 17 tumors. J Neurosurg 2011;114:1603-8.
14. Abramson DH, Marr BP, Dunkel IJ, Brodie S, Zabor EC, Driscoll SJ, *et al.* Intra-arterial chemotherapy for retinoblastoma in eyes with vitreous and/or subretinal seeding: 2-year results. Br J Ophthalmol 2012;96:499-502.
15. Muen WJ, Kingston JE, Robertson F, Brew S, Sagoo MS, Reddy MA. Efficacy and complications of super-selective intra-ophthalmic artery melphalan for the treatment of refractory retinoblastoma. Ophthalmology 2012;119:611-6.
16. Shields CL, Bianciotto CG, Jabbour P, Ramasubramanian A, Lally SE, Griffin GC, *et al.* Intra-arterial chemotherapy for retinoblastoma: Report No 1, control of retinal tumors, subretinal seeds, and vitreous seeds. Arch Ophthalmol 2011;129:1399-406.
17. Abramson DH, Marr BP, Brodie SE, Dunkel I, Palioura S, Gobin YP. Ophthalmic artery chemosurgery for less advanced intraocular retinoblastoma: Five year review. PLoS One 2012;7:e34120.
18. Thampi S, Hetts SW, Cooke DL, Stewart PJ, Robbins E, Banerjee A, *et al.* Superselective intra-arterial melphalan therapy for newly diagnosed and refractory retinoblastoma: Results from a single institution. Clin Ophthalmol 2013;7:981-9.
19. Tuncer S, Sencer S, Kebudi R, Tanyildiz B, Cebeci Z, Aydin K. Superselective intra-arterial chemotherapy in the primary management of advanced intra-ocular retinoblastoma: First 4-year experience from a single institution in Turkey. Acta Ophthalmol 2016;94:e644-51.
20. Michaels ST, Abruzzo TA, Augsburger JJ, Corrêa ZM, Lane A, Geller JI. Selective ophthalmic artery infusion chemotherapy for advanced intraocular retinoblastoma: CCHMC early experience. J Pediatr Hematol Oncol 2016;38:65-9.
21. Abramson DH, Marr BP, Francis JH, Dunkel IJ, Fabius AW, Brodie SE, *et al.* Simultaneous bilateral ophthalmic artery chemosurgery for bilateral retinoblastoma (Tandem Therapy). PLoS One 2016;11:e0156806.
22. Shields CL, Say EA, Pointdujour-Lim R, Cao C, Jabbour PM, Shields JA. Rescue intra-arterial chemotherapy following retinoblastoma recurrence after initial intra-arterial chemotherapy. J Fr Ophtalmol 2015;38:542-9.
23. Chen M, Zhao J, Xia J, Liu Z, Jiang H, Shen G, *et al.* Intra-arterial chemotherapy as primary therapy for retinoblastoma in infants less than 3 months of age: A series of 10 case-studies. PLoS One 2016;11:e0160873.

24. Magan T, Khoo CT, Jabbour PM, Fuller DG, Shields CL. Intra-arterial chemotherapy for adult onset retinoblastoma in a 32-year-old man. J Pediatr Ophthalmol Strabismus 2016;53:e43-6.
25. Shields CL, Alset AE, Say EA, Caywood E, Jabbour P, Shields JA. Retinoblastoma control with primary intra-arterial chemotherapy: Outcomes before and during the intravitreal chemotherapy era. J Pediatr Ophthalmol Strabismus 2016;53:275-84.
26. Leal-Leal CA, Asencio-López L, Higuera-Calleja J, Bernal-Moreno M, Bosch-Canto V, Chávez-Pacheco J, *et al.* Globe salvage with intra-arterial topotecan-melphalan chemotherapy in children with a single eye. Rev Invest Clin 2016;68:137-42.
27. Say EA, Iyer PG, Hasanreisoglu M, Lally SE, Jabbour P, Shields JA, *et al.* Secondary and tertiary intra-arterial chemotherapy for massive persistent or recurrent subretinal retinoblastoma seeds following previous chemotherapy exposure: Long-term tumor control and globe salvage in 30 eyes. J AAPOS 2016;20:337-42.
28. Bertelli E, Leonini S, Galimberti D, Moretti S, Tinturini R, Hadjistilianou T, *et al.* Hemodynamic and anatomic variations require an adaptable approach during intra-arterial chemotherapy for intraocular retinoblastoma: Alternative routes, strategies, and follow-up. AJNR Am J Neuroradiol 2016;37:1289-95.
29. Yannuzzi NA, Francis JH, Marr BP, Belinsky I, Dunkel IJ, Gobin YP, *et al.* Enucleation vs. ophthalmic artery chemosurgery for advanced intraocular retinoblastoma: A retrospective analysis. JAMA Ophthalmol 2015;133:1062-6.
30. Rishi P, Sharma T, Koundanya V, Bansal N, Saravanan M, Ravikumar R, *et al.* Intra-arterial chemotherapy for retinoblastoma: First Indian report. Indian J Ophthalmol 2015;63:331-4.
31. Boughton B. Intravitreal Chemotherapy for Retinoblastoma: Promising but Controversial. Eyenet 2013:31-33. Available from: http://www.aao.org/publications/eyenet/201309/ oncology.cfm. [Last accessed on 2017 Mar 10].
32. Inomata M, Kaneko A. Chemosensitivity profiles of primary and cultured human retinoblastoma cells in a human tumor clonogenic assay. Jpn J Cancer Res 1987;78:858-68.
33. Munier FL, Gaillard MC, Balmer A, Soliman S, Podilsky G, Moulin AP, *et al.* Intravitreal chemotherapy for vitreous disease in retinoblastoma revisited: From prohibition to conditional indications. Br J Ophthalmol 2012;96:1078-83.
34. Shields CL, Manjandavida FP, Arepalli S, Kaliki S, Lally SE, Shields JA. Intravitreal melphalan for persistent or recurrent retinoblastoma vitreous seeds: Preliminary results. JAMA Ophthalmol 2014;132:319-25.
35. Ghassemi F, Shields CL, Ghadimi H, Khodabandeh A, Roohipoor R. Combined intravitreal melphalan and topotecan for refractory or recurrent vitreous seeding from retinoblastoma. JAMA Ophthalmol 2014;132:936-41.
36. Brodie SE, Munier FL, Francis JH, Marr B, Gobin YP, Abramson DH. Persistence of retinal function after intravitreal melphalan injection for retinoblastoma. Doc Ophthalmol 2013;126:79-84.
37. Francis JH, Schaiquevich P, Buitrago E, Del Sole MJ, Zapata G, Croxatto JO, *et al.* Local and systemic toxicity of intravitreal melphalan for vitreous seeding in retinoblastoma: A preclinical and clinical study. Ophthalmology 2014;121:1810-7.
38. Smith SJ, Smith BD, Mohney BG. Ocular side effects following intravitreal injection therapy for retinoblastoma: A systematic review. Br J Ophthalmol 2014;98:292-7.
39. Shields CL, Mashayekhi A, Sun H, Uysal Y, Friere J, Komarnicky L, *et al.* Iodine 125 plaque radiotherapy as salvage treatment for retinoblastoma recurrence after chemoreduction in 84 tumors. Ophthalmology 2006;113:2087-92.
40. Schueler AO, Flühs D, Anastassiou G, Jurklies C, Sauerwein W, Bornfeld N. Beta-ray brachytherapy of retinoblastoma: Feasibility of a new small-sized ruthenium-106 plaque. Ophthalmic Res 2006;38:8-12.
41. Abouzeid H, Moeckli R, Gaillard MC, Beck-Popovic M, Pica A, Zografos L, *et al.* (106) Ruthenium brachytherapy for retinoblastoma. Int J Radiat Oncol Biol Phys 2008;71:821-8.
42. American Brachytherapy Society – Ophthalmic Oncology Task Force. Electronic address: Paulfinger@eyecancer.com; ABS – OOTF Committee. The American Brachytherapy Society consensus guidelines for plaque brachytherapy of uveal melanoma and retinoblastoma. Brachytherapy 2014;13:1-14.
43. Eldebawy E, Parker W, Abdel Rahman W, Freeman CR. Dosimetric study of current treatment options for radiotherapy in retinoblastoma. Int J Radiat Oncol Biol Phys 2012;82:e501-5.
44. Eldebawy E, Patrocinio H, Evans M, Hashem R, Nelson S, Sidi R, *et al.* Stereotactic radiotherapy as an alternative to plaque brachytherapy in retinoblastoma. Pediatr Blood Cancer 2010;55:1210-2.
45. Sethi RV, Shih HA, Yeap BY, Mouw KW, Petersen R, Kim DY, *et al.* Second nonocular tumors among survivors of retinoblastoma treated with contemporary photon and proton radiotherapy. Cancer 2014;120:126-33.
46. Chawla B, Hasan F, Azad R, Seth R, Upadhyay AD, Pathy S, *et al.* Clinical presentation and survival of retinoblastoma in Indian children. Br J Ophthalmol 2016;100:172-8.
47. Ali MJ, Honavar SG, Reddy VA. Orbital retinoblastoma: Present status and future challenges – A review. Saudi J Ophthalmol 2011;25:159-67.
48. Badhu B, Sah SP, Thakur SK, Dulal S, Kumar S, Sood A, *et al.* Clinical presentation of retinoblastoma in Eastern Nepal. Clin Exp Ophthalmol 2005;33:386-9.
49. Gündüz K, Müftüoglu O, Günalp I, Unal E, Taçyildiz N. Metastatic retinoblastoma clinical features, treatment, and prognosis. Ophthalmology 2006;113:1558-66.
50. Honavar SG, Singh AD. Management of advanced retinoblastoma. Ophthalmol Clin North Am 2005;18:65-73, viii.
51. Antoneli CB, Steinhorst F, de Cássia Braga Ribeiro K, Novaes PE, Chojniak MM, Arias V, *et al.* Extraocular retinoblastoma: A 13-year experience. Cancer 2003;98:1292-8.
52. Chantada G, Fandiño A, Casak S, Manzitti J, Raslawski E, Schvartzman E. Treatment of overt extraocular retinoblastoma. Med Pediatr Oncol 2003;40:158-61.
53. Chantada GL, Guitter MR, Fandiño AC, Raslawski EC, de Davila MT, Vaiani E, *et al.* Treatment results in patients with retinoblastoma and invasion to the cut end of the optic nerve. Pediatr Blood Cancer 2009;52:218-22.
54. Chantada G, Doz F, Antoneli CB, Grundy R, Clare Stannard FF, Dunkel IJ, *et al.* A proposal for an international retinoblastoma staging system. Pediatr Blood Cancer 2006;47:801-5.
55. Chawla B, Hasan F, Seth R, Pathy S, Pattebahadur R, Sharma S, *et al.* Multimodal therapy for stage III retinoblastoma (International Retinoblastoma Staging System): A prospective comparative study. Ophthalmology 2016;123:1933-9.
56. Corson TW, Gallie BL. One hit, two hits, three hits, more? Genomic changes in the development of retinoblastoma. Genes Chromosomes Cancer 2007;46:617-34.
57. Dimaras H, Gallie BL. Retinoblastoma: The prototypic hereditary tumor. In: Allgayer H, Rehder H, Fulda S, editors. Hereditary Tumors: From Genes to Clinical Consequences. Weinheim, Germany: Wiley-VCH Verlag GmbH and Co. KGaA; 2008. p. 147-62.
58. Butros LJ, Abramson DH, Dunkel IJ. Delayed diagnosis of retinoblastoma: Analysis of degree, cause, and potential consequences. Pediatrics 2002;109:E45.
59. Abouzeid H, Schorderet DF, Balmer A, Munier FL. Germline

mutations in retinoma patients: Relevance to low-penetrance and low-expressivity molecular basis. Mol Vis 2009;15:771-7.

60. Imhof SM, Moll AC, Schouten-van Meeteren AY. Stage of presentation and visual outcome of patients screened for familial retinoblastoma: Nationwide registration in the Netherlands. Br J Ophthalmol 2006;90:875-8.
61. Soliman SE, Dimaras H, Khetan V, Gardiner JA, Chan HS, Héon E, *et al.* Prenatal versus postnatal screening for familial retinoblastoma. Ophthalmology 2016;123:2610-7.
62. 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;42:2092-102.
63. Bowman RJ, Mafwiri M, Luthert P, Luande J, Wood M. Outcome of retinoblastoma in east Africa. Pediatr Blood Cancer 2008;50:160-2.
64. Kao LY, Su WW, Lin YW. Retinoblastoma in Taiwan: Survival and clinical characteristics 1978-2000. Jpn J Ophthalmol 2002;46:577-80.
65. Nyawira G, Kahaki K, Kariuki-Wanyoike M. Survival among retinoblastoma patients at the Kenyatta National Hospital, Kenya. J Ophthalmol East Cent S Afr 2013;17:15-19
66. Naseripour M, Nazari H, Bakhtiari P, Modarres-zadeh M, Vosough P, Ausari M. Retinoblastoma in Iran: Outcomes in terms of patients' survival and globe survival. Br J Ophthalmol 2009;93:28-32.
67. Chang CY, Chiou TJ, Hwang B, Bai LY, Hsu WM, Hsieh YL. Retinoblastoma in Taiwan: Survival rate and prognostic factors. Jpn J Ophthalmol 2006;50:242-9.
68. Zhao J, Li S, Shi J, Wang N. Clinical presentation and group classification of newly diagnosed intraocular retinoblastoma in China. Br J Ophthalmol 2011;95:1372-5.
69. Shields CL, Mashayekhi A, Au AK, Czyz C, Leahey A, Meadows AT, *et al.* The international classification of retinoblastoma predicts chemoreduction success. Ophthalmology 2006;113:2276-80.
70. Broaddus E, Topham A, Singh AD. Incidence of retinoblastoma in the USA: 1975-2004. Br J Ophthalmol 2009;93:21-3.
71. Survival rate and risk factors for patients with retinoblastoma in Japan. The Committee for the National Registry of Retinoblastoma. Jpn J Ophthalmol 1992;36:121-31.
72. Biswas J, Das D, Krishnakumar S, Shanmugam MP. Histopathologic analysis of 232 eyes with retinoblastoma conducted in an Indian tertiary-care ophthalmic center. J Pediatr Ophthalmol Strabismus 2003;40:265-7.