Guest editorial

Retinoblastoma: An overview of modern management

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Introduction: Retinoblastoma (RB) is an embryonic tumor originating from the retinal cells. RB is the most common intraocular cancer of childhood and accounts for 4% of all pediatric malignancies. In India, cancer is the 9th common cause for the deaths among children between 5 to 14 years of age (Satyanarayana et al, 2014). A study by Yeole BB et al, reported that RB accounts for 3.5% share of the total childhood cancers in Mumbai (Yeole and Advani, 2002). Over 95% of children with RB in the United States (USA) and other medically developed nations survive their malignancy, whereas approximately 50% survive worldwide, due to earlier detection when the tumor is still contained to the eye, whereas in underdeveloped regions, RB is often detected after it has invaded the orbit or brain (Shields and Shields, 2004). A combination of poverty, illiteracy, alternative systems of medicine and lack of access to healthcare resources account for this high rate of advanced disease in developing countries (Meel et al, 2012). Most cases of RB, however, occur in childhood with over 90% being diagnosed before five years of age; only 24 cases have been reported in adults aged between 20 years and 74 years (Singh et al, 2011) and 8 recent cases of adult onset RB have been reported (Kaliki et al, 2015). The reported worldwide incidence rate of RB in literature for children aged 0-4years varies from 3.4 per million in Bulgaria to a very high 42.5 per million in Mali and the incidence rates vary greatly in different regions (Singh et al, 2011). Unilateral RB is widely recognized to be more common (60% of all RB) and presents at an older age group than bilateral disease(Mallipatna et al, 2009) and the heritable RB presents at a younger age than the non-heritable disease. A large study in USA covering over a 30-year period from1975 – 2004 using the Surveillance Epidemiology and End Results (SEER) program database of the National Cancer Institute, found 658 cases of RB and concluded that 72% were unilateral while 27% were bilateral cases; in 1% of cases the laterality was unknown. It was concluded that with increasing age at diagnosis, the incidence of bilateral tumor decreases significantly (Singh et al, 2011). RB does not have a gender predominance predilection. The incidence of RB is variable wherein, reported incidence in USA for RB is 4.4/million for the white children, whereas in Great Britain RB affects in approximately 1 in 20000 children, 11.8 and 11.2 per million in Sweden and Finland respectively. A study was conducted by Krishna et al to study a comparison of the racial and geographic incidence patterns of retinoblastoma in North America, South America, Oceania and Europe covering a 7 year period between 1993 and 1997. They found a higher incidence of retinoblastoma in Hispanics in the USA than in white children. They also observed that rate of RB in whites in Europe was found to be the same as in Whites in USA (Singh et al, 2011).

Genetics

The discovery of the *RB1* gene at the chromosome 13q14 in the 1980s confirmed that *RB1* was the first tumor-suppressor gene. The loss of function of *RB1* initiates a retinoma and leads to cancer progression, presumably by loss of cell-cycle control and genomic stability (Dimaras et al, 2012).

RB is generally classified in three different ways: familial or sporadic, bilateral or unilateral, and heritable or non heritable. The bilateral and familial RB are caused by a germ line mutation and are called heritable tumors while unilateral sporadic RB is usually not heritable. However 10% to 15% of children with unilateral sporadic RB can have a germ line mutation. In order for retinoblastoma to develop, both copies of the gene at the 13q14 locus must be lost, deleted, mutated, or inactivated. If either the maternal or paternal copy of the inherited gene is defective, then that individual is heterozygous for the mutant allele.

Tumor formation requires both alleles of the gene to be either a mutant or inactive correlating to the "Knudsons two hit hypothesis". In familial RB, the initial event or "hit" was a germinal mutation that was inherited and found in all cells of the offspring. The second "hit" occurred sometime during development, and if it occurred in a somatic cell, such as a retinal cell, then retinoblastoma would develop and also increases the risk of secondary malignancies of the lung, bladder, bone, soft tissues, skin, and brain throughout life, especially when the children are treated with radiation. (Shields and Shields, 2004)In unilateral sporadic RB, the "two hits" occur during development of the retina and both "hits" are somatic mutations, thus less risk of secondary malignancies. Approximately 6% of newly diagnosed RB cases are familial and 94% are sporadic (Shields and Shields, 2004).

Clincial presentation

The clinical presentations for RB can vary according to the age of presentation. Leukocoria is the commonest presentation accounting for about 60%- 80% of cases, followed by strabismus in 20% of cases. Proptosis, which is a late sign of RB, is still common in developing countries compared with developed countries (Dimaras et al, 2012). In addition, glaucoma and hyphema may mimic RB (Subramaniam et al, 2014). Other presentations can be as a fungating and necrotic orbital mass, buophthalmos with an enlarged and cloudy cornea or with a flat anterior chamber (Essuman et al, 2010).

Some children with RB may have no symptoms at all. Screening in case of familial history or dysmorphic syndrome with a 13q14 deletion may lead to clinching a diagnosis of RB (Aerts et al, 2006). RB may present as life threatening problem in scenarios such as metastasis, intracranial neuroblastic malignancy (trilateral RB) or as second primary tumors (Shields and Shields, 2004).

Diagnostic modality:

1. Dilated fundus evaluation is the cornerstone for apt diagnosis of RB.
2. Ultrasonography is performed to identify and analyze the intraocular mass. Heterogeneity and calcifications provide strong evidence for the diagnosis of retinoblastoma.

3. Magnetic resonance imaging (MRI) of the brain and orbits is the most sensitive means of evaluating for extraocular extension. It gives better delineation of the optic nerve and also the pineal area.
4. A bone marrow examination and a bone scan are indicated only when the clinical examination is suggestive of metastases or a blood count abnormality is present.

Differential diagnosis

A number of ocular disorders in infants and children can clinically resemble retinoblastoma. The most common differential for pseudo-RB include, persistent hyperplastic primary vitreous, Coats' disease and ocular toxocariasis (Shields and Shields, 2004).

Classification

Two classifications are currently used for grouping intraocular retinoblastoma:

1. The Reese Ellsworth classification, according to the chance of preserving the eye using external beam radiotherapy is infrequently used in the modern era due to change in trends of preferred treatment modality.
2. The new ABC classification, according to the chance of preserving the eye using all modern therapeutic approaches. An international retinoblastoma classification (Table 1) covering the whole spectrum of the disease (from intra-retinal to the presence of overt extra-ocular extension) has been proposed (Aerts et al, 2006).

The recent classification as proposed by the American joint cancer committee (AJCC) is the TNM staging, which takes into account the clinical and pathologic tumor staging on the basis of primary tumor location (T), regional lymph node spread (N) and distant metastasis (M) (Meel et al, 2012).

Treatment methods

1. Enucleation

Primary enucleation is the choice of treatment for unilateral group E and D intraocular RB. Cases of intraocular RB that have failed on chemotherapy and conservative treatment are also treated with enucleation.

2. Focal therapy

These are used in early intraocular tumors (IIRC A–D) following chemoreduction (two to three cycles) or primarily:

a) Laser photocoagulation: It is employed for tumors not more than 2 mm in height and located posterior to equator.

b) Thermotherapy: This is a method of tumor heating, where the aim is to achieve a temperature of 42–60 degrees, which is below the coagulative threshold. It is used for tumors not larger than 3 mm in basal dimensions located at the posterior pole or mid- periphery and without any vitreous seeding. It has a synergistic effect with chemotherapy and may be used in conjunction with chemotherapy for large tumors.

c) Cryotherapy: It is used to treat equatorial or peripheral small tumors that do not exceed 3 mm in diameter and 1.5 mm in thickness.

3. Chemotherapy

In 1953, Carl Kupfer first introduced intravenous chemotherapy (IVC) for the treatment of RB. IVC is used for chemoreduction along with focal therapy for intraocular RB to facilitate globe and vision salvage, in addition, IVC is employed for orbital RB to control the malignancy prior to enucleation, for chemoprophylaxis in eyes with high-risk RB to prevent systemic metastasis, and for treatment of metastatic RB (Table:2) (Meel et al, 2012).

Vincristine, etoposide and carboplatin form the forefront as a chemotherapeutic regime of 6 cycles every 3-4 weeks, and this regime has become a widely acceptable treatment of RB. Other drugs that may be used include cyclophosphamide, melphalan and thiotepa. Chemotherapy can be used in the following manners:(Shields et al, 1996; Shields and Shields, 2004).

a) Chemoreduction: The incidence of orbital RB varies from 6% to 8% in developed countries and 5-44% in developing countries. The treatment with chemoreduction aims to reduce the tumor volume in large intraocular tumors (IIRC Group B to D), thereby allowing use of less-damaging and more focused therapeutic measures in order to preserve vision and avoid enucleation. The most common chemotherapy protocol used currently consists of vincristine, etoposide and carboplatin. Following two cycles of chemotherapy, Shields *et al*. have reported a 35% decrease in the mean base diameter, 50% decrease in the tumor thickness and complete resolution of sub-retinal fluid in 76% cases (Abramson, 1990). It is believed that less than six cycles of chemoreduction may not be sufficient to completely destroy sub-retinal seeds which was reported by Shields et al who noted 0% recurrence after 6 cycles of chemotherapy (Ali et al, 2011). The major problem with systemic chemotherapy is the recurrence of vitreous and sub-retinal seeds because of limited penetration of systemically administered chemotherapeutic agents into the sub-retinal and vitreous spaces, which are avascular.

Adjuvant chemotherapy

Certain histo-pathological features (iris, ciliary body, choroid (massive), sclera and optic nerve beyond lamina cribrosa) in the enucleated eyes are associated with a higher risk of systemic metastasis and/ or local recurrence. Adjuvant treatment in these cases reduces the likelihood of local recurrence and distant metastasis. Additionally, extra-scleral and optic nerve cut-end involvement is classified as microscopic residual disease and is treated with 12 cycles of adjuvant chemotherapy and EBRT (Meel et al, 2012).

Neo- Adjuvant Chemotheapy (NACT)

NACT is used to reduce the tumor size, followed by enucleation, local radiotherapy and adjuvant chemotherapy, to complete a total of 6 cycles and causes rapid reduction in tumor bulk and also controls micro-metastatic disease. The tumor reduction enables the option of enucleation versus exenteration. The overall survival rate reported in patients with extraocular disease is 50–70% in patients with extraocular retinoblastoma. The data from India shows an overall survival of 50% at 18 months of follow-up (Ali et al, 2011).

High-dose chemotherapy with autologous stem cell rescue (ASCR)

It is beneficial for some cases of metastatic RB as metastatic RB is more common in developing countries (9-11%) than developed countries (5-6%). Dunkel et al treated 13 patients with trilateral RB using induction chemotherapy with VEC and cyclophosphamide in addition to high-dose chemotherapy with thiotepa-based or melphalan and cyclophosphamide with ASCR and prevented death in 38% cases without the need of EBRT at 6 years follow-up. Beneficial effects were seen in cases with central nervous system (CNS) metastatic disease with high-dose chemotherapy and ASCR with survival in 40% cases (2 of 5 cases) at a mean follow-up period of 6 years (Kaliki and Shields, 2015).

Periocular Chemotherapy

It allows higher effective doses at these sites, establishing effective treatment while limiting the systemic side effects of chemotherapy. Periocular carboplatin has been most commonly used and reported to have promising therapeutic benefit in the treatment of groups C and D RB. It is associated with serious adverse effects, including ocular motility changes, orbital fat necrosis, severe pseudo-preseptal cellulitis and ischemic necrosis with atrophy of the optic nerve resulting in blindness (Kiratli et al, 2007; Mulvihill et al, 2003). These side-effects are thought to result from a rapid dispersal of the chemotherapeutic agent.

Intra-arterial chemotherapy (IAC)

Recently, IAC injection is being used enthusiastically for treating RB as it provides control of tumor, resolution of retinal detachment, globe salvage with minimal side effects. Reese et al, were the first to investigate IAC for RB by intracarotid administration of triethylene melamine in 1958. In 1990's, Kaneko described the selective ophthalmic arterial injection of melphalan by distal occlusion of internal carotid artery with a balloon catheter (Kaliki and Shields, 2015; Shields and Shields, 2004). This technique was further modified by Abramson et al by supra-selective IAC involving injection of melphalan directly into the proximal portion of the ophthalmic artery. The various agents used for IAC in RB include melphalan, carboplatin, topotecan, and methotrexate. Shields et al reported their experience in 70 consecutive patients treated with supra-selective IAC and concluded 72% globe salvage rates when used as primary treatment and 62% globe salvage rate when used as secondary treatment. The various complication associated with IAC are transient neutropenia, carotid spasm, temporary side-effects include periorbital edema, periocular hyperemia, madarosis, and ocular dysmotility. Severe complications include vitreous hemorrhage in 13-27%, retinal detachment (RD) in 15 to 27%, retinal pigment epithelial changes occur in 5-53%, retinal ischemia in 4-24%, and chorioretinal atrophy in <1 to 29% cases. These complications were attributed to changes occurring secondary to the drug related toxicity or competency of ophthalmic artery catheterization causing structural and vascular damage of the retina (Kaliki and Shields, 2015).

Intravitreal chemotherapy

Ericson and Rosengren first investigated the use of intravitreal chemotherapy for RB in 1960's. After serial analytical tests for 20-30 ug melphalan, it was approved as the drug of choice for intravitreal chemotherapy, with minimal ocular complications and no significant electroretinogram changes. Intravitreal melphalan 20-30 ug was injected every month via the pars plana approach with concomitant triple freeze-thaw cryotherapy to the injection site. The distance of the site of injection from the limbus depends upon the age of the child.

The most concerning side-effect of intravitreal chemotherapy is extraocular tumor spread. Extraocular tumor spread can be prevented, by selection of injection site to avoid injection directly into the contaminated posterior chamber, no anterior chamber paracentesis to create a transient hypotony and avoid reflux of contaminated vitreous at the injection site secondary to variations in intraocular pressure; triple freeze-thaw cryotherapy at the injection site; and injecting a bleb of subconjunctival chemotherapy (carboplatin) prior to intravitreal chemotherapy. The other serious side-effects include iris atrophy, vitreous hemorrhage, RD, and chorioretinal atrophy. Minor side-effects include transient conjunctivitis, transient keratitis, corneal edema, cataract, ocular inflammation, vitreous condensation and banding, and retinal pigment epithelial changes (Kaliki and Shields, 2015; Meel et al, 2012).

5. Radiotherapy

RB is a radiosensitive tumor and responds well to radiotherapy.

a) Brachytherapy: It is indicated in cases of peripheral tumors up to 15 mm in diameter and 7–8-mm thick, possibly with localized vitreous invasion over the tumor. It involves placing a radioactive implant on the sclera over the base of RB. A total of 40 gray (Gy) is delivered over a period of 2-4 days. It forms a part of both primary and secondary treatment after prior failed treatments. Approximately 80% tumor control can be achieved. The complications reported are radiation maculopathy and papillopathy (Shields and Shields, 2004).

b) External beam Radiotherapy: Is a method of delivering irradiation to the whole eye in treating advanced RB, especially with the presence of vitreous seeds. A dose of 45 Gy is delivered to the target volume by two electron beams over 5 weeks, with fractions of 1.8 (for children under 12 months old) to 2Gy (for children over 12 months) (Meel et al, 2012). It can be achieved with the whole eye technique and the lens sparing technique. The complications reported are radiation damage to retina, optic nerve and the lens. EBRT can induce second cancers in the field of irradiation (Shields and Shields, 2004).

Management of Extra-ocular RB

Patients with extraocular disease have a very poor prognosis with respect to survival. There has been encouraging data to suggest that patients with regional extraocular disease may benefit from a combination of conventional chemotherapy and EBRT. All those with distant metastatic disease may benefit from high-dose chemotherapy

and EBRT in conjunction with bone marrow stem cell transplantation. Chantada et al reported a 5-year event free survival rate of 84% in 15 patients with orbital or pre-auricular disease treated with chemotherapy with EBRT.

Patients with metastatic extraocular disease have a poor prognosis when treated with regimens of conventional doses of chemotherapy. The proposed trial by the children's oncology group for patients with metastatic disease involves conventional chemotherapy, stem cell harvest, high-dose chemotherapy with stem cell rescue and EBRT of involved sites. However there is a high risk of developing secondary tumors with children less than 1 year of age (Chintagumpala et al, 2007).

Genetic counseling

Genetic counseling in families with RB is an important aspect in their care and should be coordinated with a medical geneticist or genetic counselor who is a part of the RB team. The identification of genetically susceptible family members can lead to early diagnosis and avoid the need for enucleation of the affected eye.

Genetic analysis provides important information with regard to the risk for parents to have additional children with RB. Genetic testing for *RB1* mutations is clinically available in certified DNA diagnostic laboratories and can detect constitutional mutations in approximately 90% of patients with bilateral disease. Patients with bilateral disease can be assumed to have a constitutional mutation and DNA obtained from a blood sample is examined directly for mutations. Children with unilateral tumors may or may not have a germline constitutional mutation and for these cases, a frozen tumor specimen and a blood sample is sent for analysis. There are a wide variety of different *RB1* mutations, including whole gene deletions, and small frameshift, nonsense, splice site, and missense mutations. Somatic changes can also include silencing of the *RB1* promoter by methylation. Mutations identified in the tumor are then studied in a DNA sample obtained from blood and the presence of a mutation in blood is presumptive evidence of a germline or constitutional mutation. Identification of the same mutation in another young family member should prompt frequent evaluations by an ophthalmologist using appropriate examination techniques.

Knowledge of the specific mutation identified in the family has also been used to perform pre-implantation genetic diagnosis in order to implant in vitro fertilized embryos that are unlikely to carry the mutation. Even with extensive molecular analysis, the causative mutation is not always identified. In these cases, if there are multiple family members with retinoblastoma, then predictive genetic testing can be performed by linkage analysis using polymorphic markers that flank the *RB1* gene, a technique also referred to as indirect genetic testing (Chintagumpala et al, 2007; Shields and Shields, 2004).

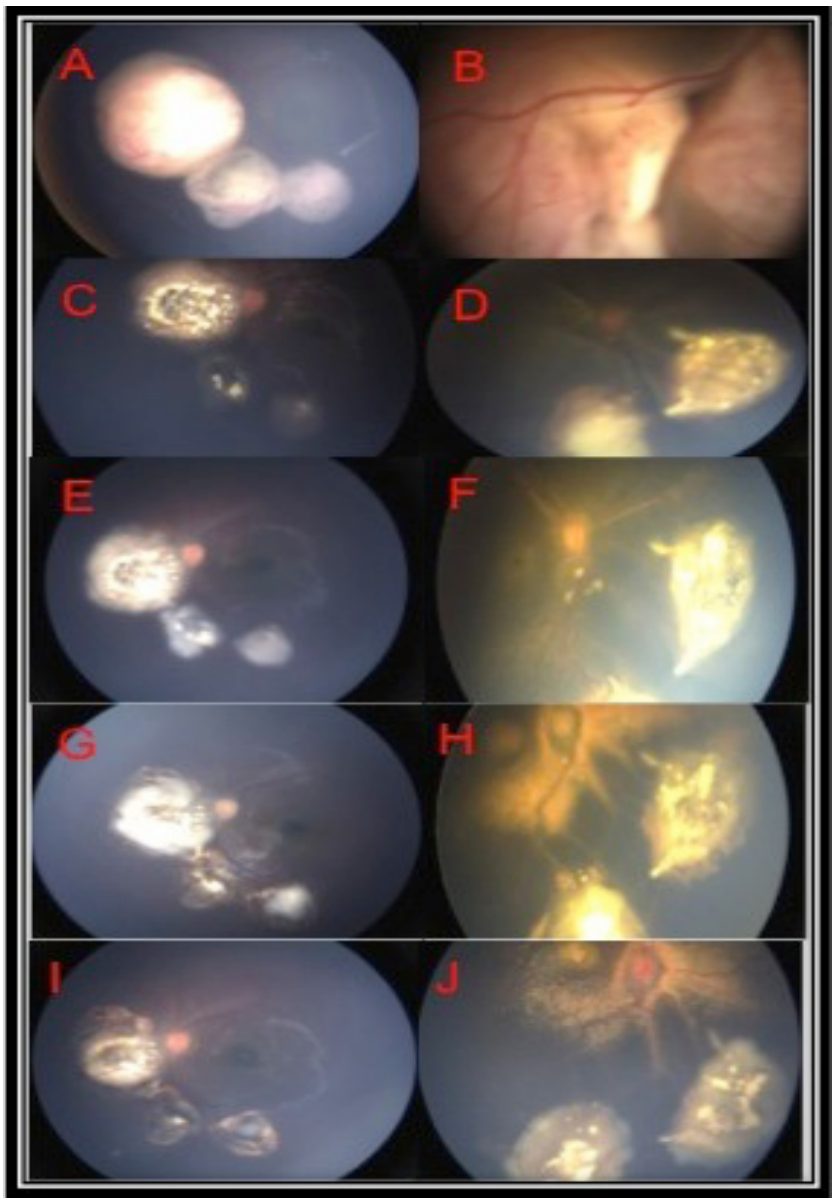

Figure A: J shows the regression of tumor with focal and systemic chemotherapy

Figure A and B show the left eye with group B RB and right eye group D RB of a patient. Figure C and D shows regression of tumor post chemotherapy 1st cycle. Figure E is post trans-pupillary thermotherapy and F shows regression of retinal detachment after 2nd cycle of chemotherapy. FigureG-J show regression of tumor with 3rd and 4th chemo cycle with TTT.

Table 1: International intraocular retinoblastoma classification (IIRC)

RB-Group	Sub group	Reference	Features
A	Very low risk	Small tumor	• ≤ 3mm in size and • > 1.5mm from the disc • >3mm from the foveola
B	Low risk	Eyes with no vitreous or subretinal seeding and discrete retinal tumor of any size or location	• Tumors not in group A • No vitreous or subretinal seeding SRF >5 mm from the base of the tumor
C	Moderate Risk	Eyes with only focal vitreous or subretinal seeding and discrete retinal tumors of any size and location	• Seeding local, fine and limited • Treatable with a radioactive plaque • Tumors discrete and of any size and location, • Up to one quadrant of SRF
D	High Risk	Eyes with diffuse vitreous or subretinal seeding and/ or massive, non-discrete endophytic or exophytic disease. Eyes with more extensive seeding than Group C	• Massive and/or diffuse intraocular disseminated disease • More than one quadrant of retinal detachment • Fine greasy vitreous seeding or avascular masses • Subretinal seeding, plaque-like
E	Very high risk	Eyes that have been destroyed anatomically or functionally by the tumor. Eyes with one or more than the following	• Irreversible neovascular glaucoma • Massive intraocular hemorrhage • Aseptic orbital cellulitis • Tumor anterior to anterior vitreous face • Tumor touching the lens • Diffuse infiltrating retinoblastoma • Phthisis or prephthisis

(*SRF= Subretinal fluid)

Table 2: Indications of chemotherapy

Chemotherapy	Indications
Intravenous	Intraocular RB especially bilateral cases
	Orbital RB
	High-risk RB
	Metastatic RB
Intra-arterial	Intraocular RB as primary treatment
	Refractory intraocular RB as secondary treatment
Periocular	Recurrent or residual vitreous seeds
	Bilateral RB with poor prognosis at diagnosis
	In cases with contraindication of systemic chemotherapy
Intravitreal	Recurrent or residual vitreous seeds

Conclusion

The staging and early intervention in the treatment of RB leads the battle for the prognosis of globe salvage and for the survival of the child. The treatment still continues to be a challenge both diagnostically and therapeutically. It is important to first clearly establish a correct diagnosis before embarking on therapy as many factors enter into management decisions such as patient age, tumor laterality, size, location, and extent, and anticipated visual prognosis. Chemotherapy has lead the modern era in managing RB from darkness to light, but enucleation still holds it ground for managing advanced tumors.

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