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Chapter

Retinoblastoma: Update on Current Management

Abdullah Almater, Abdulrahman Alfaleh, Khalid Alshomar and Saleh AlMesfer

Abstract

Retinoblastoma (Rb) is the most common primary intraocular malignancy in children with an incidence from 1:15,000 to 1:20,000 live births. It can present as a unilateral or bilateral involvement of the eyes. It is generally induced by biallelic mutation of the RB1 tumor suppressor gene that leads to malignant transformation of primitive retinal cells. The most common presentation is leukocoria, followed by strabismus. The initial assessment and future treatment of such tumor should be based on the laterality, the stage of the tumor, and the presenting age of the child. In general, the primary target of therapy is to preserve the child's life. However, preserving the globe and preserving vision should be achieved whenever it's possible. Retinoblastoma treatment has evolved from enucleating the affected globe to also involving external beam radiation therapy, cryotherapy, laser photocoagulation, thermotherapy, brachytherapy, and chemotherapy (intravitreal, intra-arterial, and systematic). This chapter is intended to discuss briefly the clinical presentation of Rb, as well as a comprehensive review about the evolution and current treatment modalities with a focus on cases with low-risk features.

Keywords: retinoblastoma, management, enucleation, external beam radiation therapy, brachytherapy, thermotherapy, laser photocoagulation, cryotherapy, chemotherapy

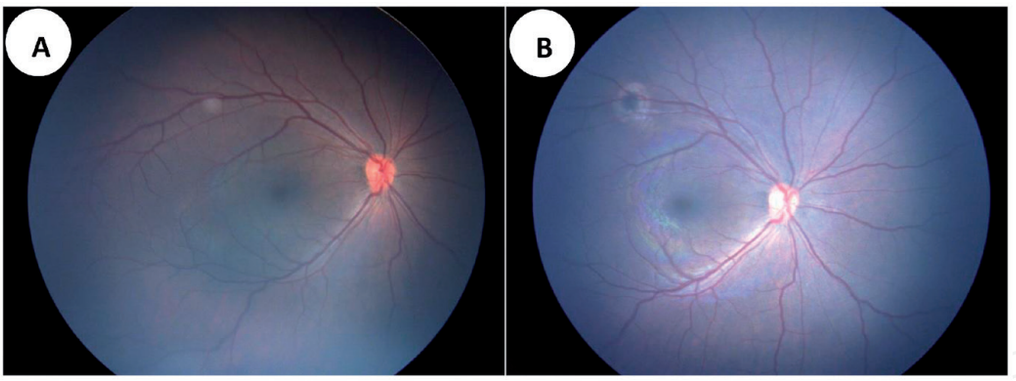
1. Clinical presentation and diagnosis

The clinical presentation of retinoblastoma can be variable depending on the stage of the tumor. However, the most common presenting symptom overall is abnormal white reflection from one or both pupils [1]. This can be observed grossly by the naked eye and is termed as leukocoria. The second most common presentation of retinoblastoma is strabismus, which results from sensory deprivation when the tumor involves the central vision [2]. Less commonly, uveitis, glaucoma, hyphema, iris heterochromia, and orbital cellulitis can also be presenting signs for retinoblastoma [3]. A more advance and late presentation may result in proptosis and orbital swelling [4]. Any of the mentioned clinical presentations in a child should prompt detailed clinical exam including dilated fundus examination. Typically, it shows unifocal or multifocal white vascularized retinal mass with or without tumor seeding. Different imaging modalities can be performed to aid in the diagnoses of retinoblastoma. The most easy and readily available modality is ultrasound. It can be helpful in the detection of intraocular mass characteristic

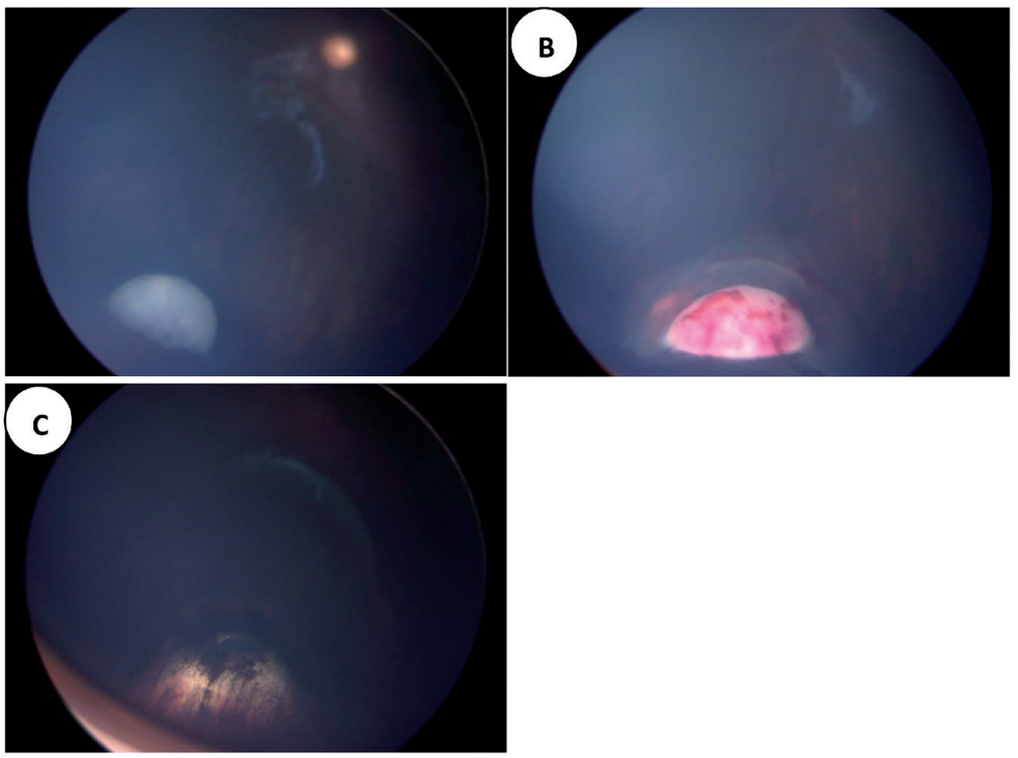
(height, thickness, and depth) and the presence of heterogeneity and calcification. Computed tomography (CT) is more sensitive in detecting intraocular calcification and delineating the mass. However, CT scan raises the concern of developing secondary malignancies in cases with germ line mutation due to radiations [5]. Magnetic resonance imaging (MRI) is currently the preferred imaging modality of choice for most ophthalmologists. MRI is considered the best for detecting optic nerve involvement and extraocular extension [6]. Other diagnostic procedures like cerebrospinal fluid (CSF) analysis and cytology are particularly performed when there is evidence of optic nerve involvement grossly or microscopically based on histopathologic examination after enucleation. Bone marrow biopsy is indicated for bone marrow metastasis based on clinical exam or blood work-up. Diagnosis of retinoblastoma should be based on clinical examination that is supported by imaging techniques. However, differentiating retinoblastoma from other conditions like persistent hyperplastic primary vitreous (PHPV), Coats' disease, or toxocariasis can be challenging [7–11]. Different classifications have been proposed for retinoblastoma staging throughout the past decades, including TNMH (tumor, node, metastasis, heritable trait) cancer staging for the American Joint Committee on Cancer (AJCC), Reese-Ellsworth classification system (R-E), and International Intraocular Retinoblastoma Classification (IIRC) [12–16]. The International Intraocular Retinoblastoma Classification or International Classification of Retinoblastoma (ICRB) have been widely accepted by ophthalmologists since they were first introduced in 2003, to predict the outcomes following chemoreduction for retinoblastoma [15, 16] (**Table 1** and **Figure 1**).

Group	Subgroup	Reference	Features
A	Very low risk	Small tumor	• RB ≤3 mm (in basal dimension) • Al least 3 mm away from the foveola and 1.5 mm from the optic nerve • No vitreous or subretinal seeding is present
B	Low risk	Larger tumor Macula Juxtapapillary Subretinal fluid	• RB >3 mm (in basal dimension) • Macular location (≤3 mm to foveola) • Juxtapapillary location (≤1.5 mm to optic nerve) • Additional subretinal fluid (≤3 mm from margin) • No vitreous or subretinal seeding is present
C	Moderate risk	Focal seeds	• Focal subretinal and/or vitreous seeds ≤3 mm from the tumor
D	High risk	Diffuse seeds	• Diffuse subretinal and/or vitreous seeds >3 mm from the tumor
E	Very high risk	Extensive retinoblastoma	• Extensive retinoblastoma occupying >50% of globe or any of the following: • Secondary neovascular glaucoma • Tumor anterior to anterior vitreous face or touching the lens • Diffuse infiltrating retinoblastoma • Massive intraocular hemorrhage • Aseptic orbital cellulitis • Phthisis bulbi

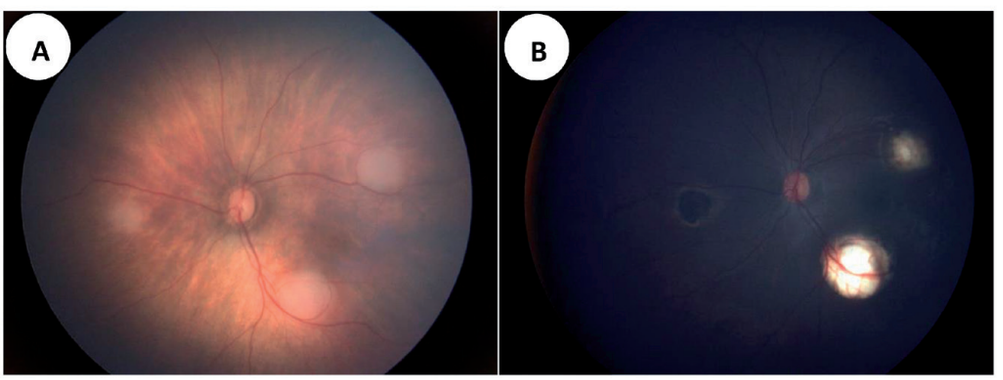
Table 1.
International intraocular retinoblastoma classification.



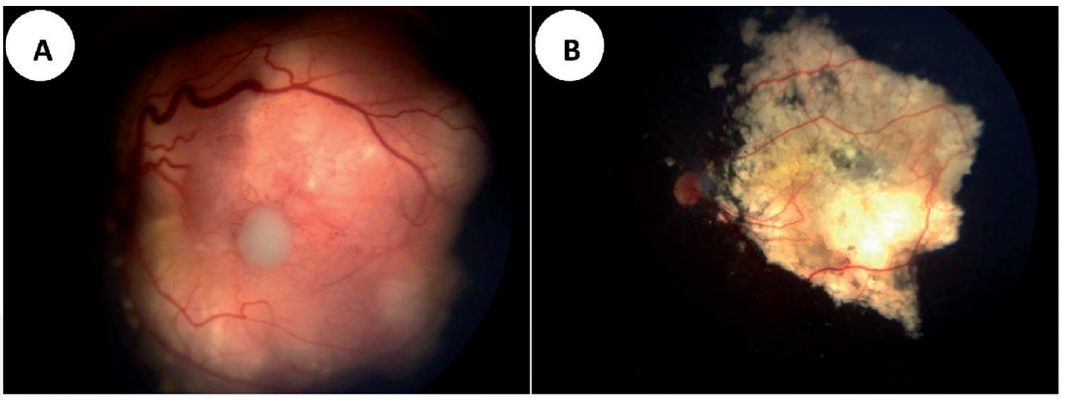
Case 1: One-month-old female with strong family history of retinoblastoma that was diagnosed with unilateral retinoblastoma through family screening program. (A) Showing single active lesion along the continuation of the superior-temporal arcade in the right eye (group A). (B) Showing the same lesion 1-month post-TTT.



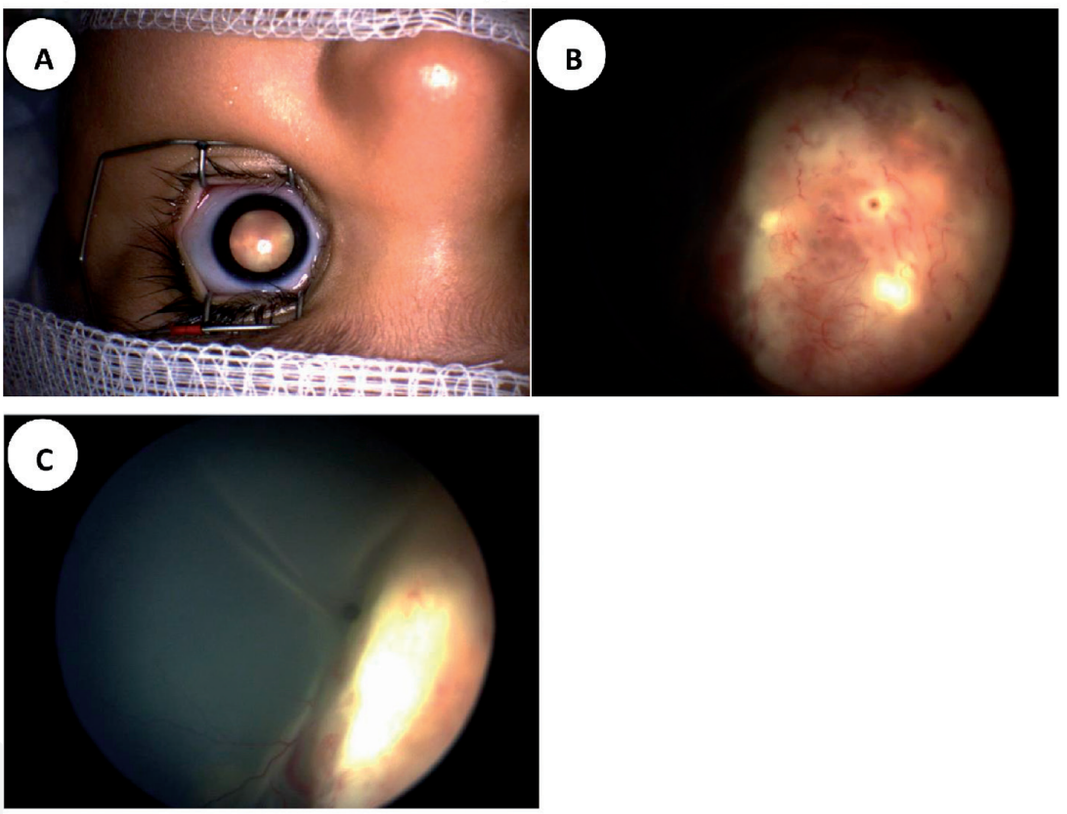
Case 2: Two-year-old male with bilateral retinoblastoma (OD, group E; OS, group A). (A) Single thick whitish lesion located inferior-temporal in the left eye (group A). (B) Same lesion with hemorrhages post-cryotherapy and TTT in the same month. (C) Flat scarred lesion after 3 months. Right eye photos are not shown here.



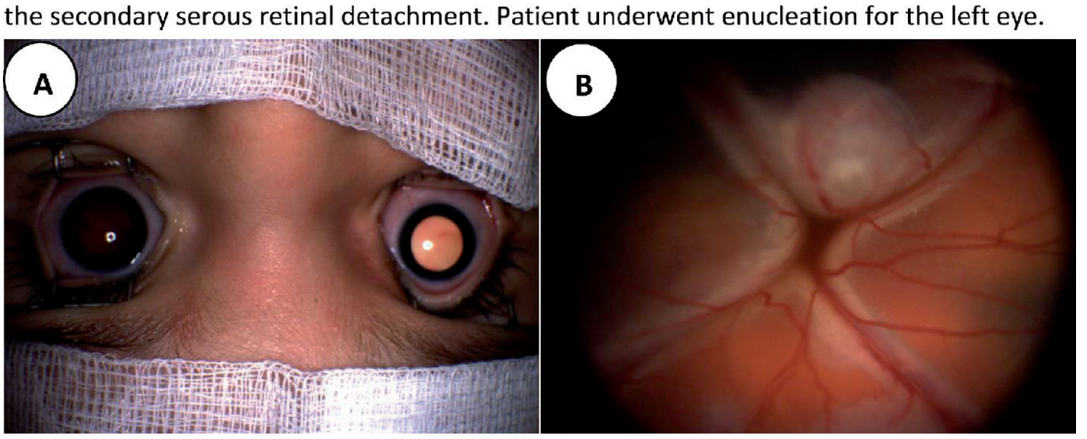
Case 3: Twenty-eight-day-old male diagnosed with bilateral retinoblastoma (group B). (A) Left eye showing three active whitish lesions (one large macular lesion measuring >3 mm in size, two smaller lesions at superior-temporal arcade and inferior-nasal arcade (group B)). (B) Flat and scarred lesions 3 years post-TTT and intravenous chemotherapy. Right eye photos are not shown here.

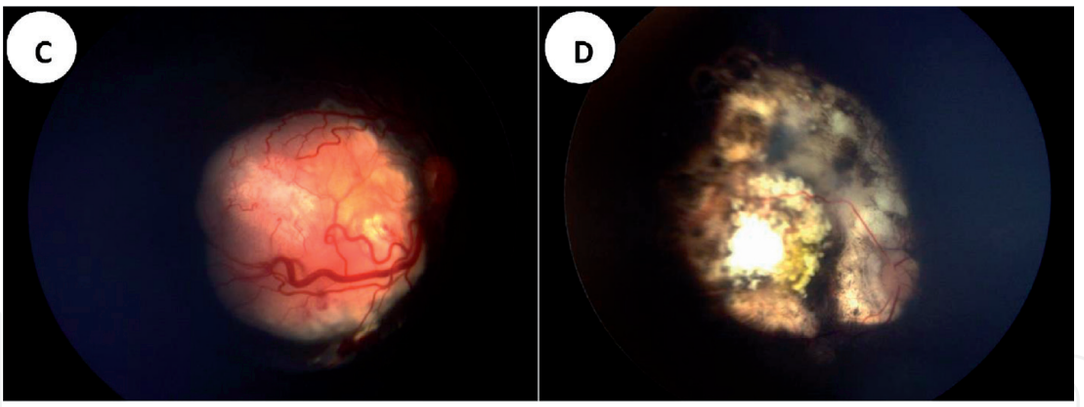


Case 4: Eight-month-old female with unilateral sporadic retinoblastoma. (A) Left eye showing large subretinal macular lesion, with initial subretinal seeding (group C). (B) Similar lesion showing regressing and calcification (cottage cheese appearance) 2 years after multiple TTT and intravenous chemotherapy.



Case 5: Five-month-old male with unilateral retinoblastoma. (A) External photo of the left eye showing leukocoria. (B) Left eye showing large temporal and inferior-temporal lesion with calcification and secondary retinal detachment (group D). (C) Fundus photo showing the secondary serous retinal detachment. Patient underwent enucleation for the left eye.





Case 6: Eight-month-old male with bilateral retinoblastoma (OD, group C; OS, group E). (A) External photo of both eyes showing leukocoria in the right eye and dim reflex for the left eye. (B) Fundus photo of the left eye showing large whitish lesion in the posterior pole with total retinal detachment (group E). (C) Right eye showing large vascularized elevated whitish lesion involving the macula. (D) Scarred macular lesion 14 months post-TTT and intravenous chemotherapy. The patient underwent enucleation of the left eye.

Figure 1.
Retinoblastoma tumors, according to the international intraocular retinoblastoma classification, and their response to treatments.

2. Management

Management of retinoblastoma is complex and requires a multidisciplinary team approach that includes an ophthalmologist, pediatric oncologist, radiation oncologist, pathologist, geneticist, social worker, nurses, and others. The primary goal of treatment is to save the child's life and then to salvage the globe and optimize the vision if possible. A multimodal therapeutic option for retinoblastoma is available, which ranges from focal therapies like laser photocoagulation, cryotherapy, thermotherapy, and plaque radiotherapy to enucleation or chemotherapy for more advance cases. The decision for choosing a treatment option is depending on several factors including the laterality, tumor size and histopathologic feature, the age and general health of the child, and the family desires.

3. Enucleation

Enucleation is the preferred option for most children presenting with advance tumor (group E eyes), especially if unilateral [17–21]. Other indications for enucleation are failure of all possible effective therapies, active tumor in an eye with no visual potential, anterior segment invasion, secondary neovascular glaucoma, and when the visualization of the tumor is compromised due to corneal opacity, cataract, or vitreous hemorrhage [22]. Enucleation is rarely indicated for bilateral retinoblastoma due to devastating functional limitation that follows such decision. The goal during enucleation is to obtain as much optic nerve as possible (usually 8–12 mm) to make sure that the surgical margin is free from tumor [23, 24]. Surgeons should avoid perforation of the globe during the procedure to minimize the potential risk of tumor seeding into the orbital tissue [25]. Histopathologic evaluation post enucleation allows for evaluation of high-risk features that requires additional chemotherapy. These features include retrolaminar optic nerve invasion,

choroidal invasion, scleral and orbital invasion, and anterior chamber seeding [26–28]. At the time of enucleation, an orbital implant is placed to ensure proper growth of the orbit and allows for free movement of the prosthesis when attaching the extraocular muscles to the implant [4, 29]. Many different orbital implants can used and are generally divided to porous and nonporous implants. The most commonly used are porous implants, hence allowing vascular growth in the tiny pores within the implant. This can serve in the stabilization of the implant while minimizing the risk of exposure and extrusion or infection [4, 25].

4. External beam radiation therapy (EBRT)

External beam radiation therapy is an important modality used in the treatment of retinoblastoma. However, due to serious adverse effects, it has fallen out of use and became preserved for moderately advanced disease where retinoblastoma is refractory or progressive after chemotherapy to salvage the eye from enucleation. EBRT techniques have improved overtime, and new methods aim to eliminate the disease and minimize normal tissue exposure to avoid any adverse effects [30–33].

The main EBRT techniques used in treating retinoblastoma are photon or electron radiation therapy (ERT), intensity-modulated radiation therapy (IMRT), and proton radiation therapy (PRT). IMRT and PRT allow for more conformal radiotherapy options in addition to a unique physical property of PRT. Rather than traversing the target, protons stops at energy-dependent depth and with a reduced exit dose to almost zero where it reduces the injury to uninvolved structures and limit the radiation beams to a specific area. This physical property has shown to decrease unwanted adverse effects, making PRT become superior to photon therapy [30, 31].

EBRT treatment sessions are usually scheduled over a period of weeks where multiple small fractions of radiation are delivered via an external machine targeting the lesion. This increases tumor sensitivity to radiation by allowing time for reoxygenation and reassortment of cell cycle. It also spares normal tissues by allowing time for repair in between fractions. Conversely, PRT is delivered in one or a few large fractions, but to small discrete volumes, hence minimizing the volume of surrounding irradiated normal tissue [30, 34].

The outcome of patients who were treated with EBRT has been studied over the past decades. Enucleation was ultimately required in 18–37.5% of eyes, and local failure after radiotherapy was similar between PRT and ERT. Vision was preserved in most of the cases with an outcome showing up to 70% of patients having no or mild visual impairment. Moderate visual impairment is seen in 10–23% of eyes, whereas poor or no useful vision was in 20–41.7% of non-enucleated eyes. The best visual outcomes are noted in patients with early stages that spared the optic disc, macula, and fovea, suggesting that the location of tumors has an impact of visual outcome even after PRT [35–38].

Acute toxicities that can be seen after therapy sessions include local erythema of the skin, hyperpigmentation, erythema of the conjunctiva, and loss of eyelashes. Patients treated with PRT had a similar rate of acute toxicities, compared to patients treated with ERT. Cataracts were the most common long-term complication in eyes treated with EBRT. Other ocular complications noted are radiation retinopathy, glaucoma, neovascularization, vitreous hemorrhage, retinal detachment, strabismus, and less common toxicities [35–38].

The hypothalamus-pituitary axis is known to be affected in EBRT as it is exposed to radiation beams. Growth hormone deficiency and thyroid-stimulating hormone abnormality are noted in patients treated with EBRT. However, due to PRT physical properties that eliminate the radiation to midline structures, these adverse effects

are noted to be less than in conventional radiation therapy. Therefore, endocrinopathies were almost limited in patients treated with PRT [38, 39].

Another adverse effect reported is craniofacial deformities where the facial and bony structures tend to be affected in EBRT. These include hypoplasia, hyperpigmentation, or soft tissue fibrosis. Long-term dentofacial anomalies have also been reported [36, 38, 40].

Risk of new cancers is a major concern in retinoblastoma patients treated with radiotherapy. The cumulative incidence of a second cancer at 50 years after diagnosis of retinoblastoma was 36% for hereditary retinoblastoma. Bone, nasal cavity, connective and soft tissue, and other neoplasms have been associated in retinoblastoma survivors who received EBRT. Osteosarcomas and soft tissue sarcomas are the most common tumors reported in irradiated patients reaching up to 76% of all cancer in ages younger than 25 years old. On the other hand, in unilateral retinoblastoma patients who did not receive radiation, sarcomas did not occur. In addition, the subsequent risk of cancer was noted to be higher in irradiated patients than nonirradiated whether the patients had hereditary or non-hereditary disease. Also, elevated doses of radiation were associated with increased risk of subsequent tumors. However, no subsequent cancers were noted among hereditary patients treated with chemotherapy. Furthermore, a comparison between photon and proton radiotherapy techniques was done and it showed that the 10-year cumulative incidence of malignancies was significantly higher in photon therapy compared to proton therapy. Therefore, patients treated with radiotherapy should have long follow-ups regardless of the modality used [32, 33, 41].

Lastly, the quality of life was observed, and no difference was noted between children and their parents regarding the quality-of-life outcomes compared to the general population [38].

5. Brachytherapy

Brachytherapy is a form of radiotherapy where a source of radiation is placed inside or next to the treatment area. In retinoblastoma the radioactive implant is placed on the sclera corresponding to the tumor base and fixed surgically to irradiate the tumor. Implantation technique requires excellent surgical skills and is applied under general sedation where the implant is fixed on the sclera and maintained for few days and removed with the patients remaining in the hospital during the entire treatment [42]. Iodine-125 and Ruthenium-106 are the most common radioactive agents to be used in intraocular lesions. Other agents can be used such as Ruthenium-106, Palladium-103, Strontium-90, Cobalt-60, and Iridium-192 [42, 43]. Like EBRT, the use of brachytherapy has been limited to progressive disease and to preserve the eye from enucleation. However, brachytherapy offers less spread of radiation, and its complications that can be associated with EBRT can be prevented where damage of normal tissue can be minimized which can lead to deformities and more importantly reduce the risk of radiation-induced second cancers [42, 44, 45]. Brachytherapy can be used as primary modality to treat retinoblastoma where the tumor is found solitary and located anterior to the equator as per the American Brachytherapy Society-Ophthalmic Oncology Task Force (ABS-OOTF) recommendations. As for secondary treatment where retinoblastoma failed to respond to other treatment modalities, it can be used irrespective of its location [43]. Brachytherapy is also an effective method that can be used post enucleation to prevent recurrence [46].

Plaque brachytherapy achieved tumor control in 83–89% of cases in some studies reaching up to 88% when used as a primary modality and appears to be the best choice in patients who failed laser photocoagulation, thermotherapy, cryotherapy, or chemoreduction, but it is less successful in patients who failed EBRT [45, 47, 48].

Reirradiation of local recurrence with brachytherapy can be considered as an option to salvage the eye from enucleation, and it may provide tumor control and eye preservation [48]. Complications related to radiation included radiation retinopathy, maculopathy, papillopathy, cataract, and glaucoma. Fortunately, no second cancers related to plaque brachytherapy were reported in the literature [45, 47–50].

Visual acuity in patients was found to be good in 64% and poor in 24–32% of non-enucleated eyes who were treated with plaque radiotherapy. The poor visual outcome was mainly associated with macular lesions, macular edema, vitreous hemorrhage, and phthisis bulbi. It appears that there is no significant difference whether brachytherapy was used as a primary or secondary modality in visual outcome [45, 47].

In many centers, Iodine-125 is used as the standard isotope for plaque brachytherapy. This is due to the physical properties like its half-life, low energy, adequate dose distribution, and ease of shielding [42, 43]. In a study, the use of Iodine-125 as salvage treatment in 84 recurrent lesions after chemoreduction is reported. It showed 95% control in those who failed chemoreduction and 100% control in patients who failed a combination of chemoreduction and EBRT. Complications were higher in patients who received EBRT and included papillopathy, vitreous hemorrhage, cataract, and neovascularization [50].

Ruthenium-106 has some advantages over Iodine-125 where it's lower in cost, has longer half-life, and is safer in terms of radioprotection. It has shown tumor control achievement up to 73%, and some studies achieved eye preservation in 89% of cases. Local recurrence with Ruthenium-106 is noted to reach 6.3%. Complications of Ruthenium-106 are generally similar to those found in other radiation modalities such as proliferative retinopathy which can lead to vitreous hemorrhage, radiation maculopathy radiation optic neuropathy, exudative retinal detachment, neovascularization, neovascular glaucoma, and cataracts. Previous treatment with EBRT was shown to be associated with increased risk of some complications such as optic neuropathy, retinal detachment, and cataracts. However, studies of efficacy of Ruthenium-106 in retinoblastoma compared to Iodine-125 are limited in the literature [51–54].

6. Focal therapy

Focal therapy in treatment of retinoblastoma is used either alone in small retinoblastomas (group A or B) (1, 2 laser) or after chemoreduction, usually after two or three cycles, or for small recurrent tumors or subretinal seeds [55–57].

7. Transpupillary thermotherapy (TTT)

Thermotherapy is based on increasing the tissue temperature from 45 to 60°C to induce a cytotoxic effect, through applying an 810-nm diode laser below the coagulative threshold to prevent retinal vessels from coagulation, and it can be used alone for small retinoblastomas that are 3 mm in diameter without vitreous or subretinal seeds [57, 58]. In a study of 91 tumors, 92% of the tumors that were 1.5 mm in diameter were controlled with thermotherapy alone [59]. Out of 188 treated by thermotherapy, complete regression of the tumor was achieved in (85%) 161 tumors, where the mean tumor size is 3.0 mm base and 2.0 mm thickness [60]. Complications of transpupillary thermotherapy include iris atrophy, cataracts, tumor seeding into the vitreous, retinal fibrosis, transition, and vascular occlusion.

8. Laser photocoagulation

Laser photocoagulation is aimed to diminish blood supply of tumor. This type of treatment is used for small (4 mm in diameter and 2 mm in thickness) and posterior tumors. Argon or diode laser or a xenon arc is used but not directly on tumor tissue; instead it is aimed to coagulate the blood vessels that supply the tumor.

Retinal detachment, retinal vascular occlusion, retinal traction, and preretinal fibrosis can be a complication of this type of treatment [61–63].

9. Cryotherapy

Cryotherapy induces rapid decrease (freeze) of tumor tissue, and this will cause damage to the tumor blood vessel endothelium and lead to vascular thrombosis, which results in tumor ischemia and infarction. It is used as primary treatment for small equatorial and peripheral retinal tumors (<3.5-mm base and <2-mm thickness). Treatment protocol is based on three applications for each session every 4–6 weeks until complete regression of the tumor. Complications of cryotherapy include retinal tears and detachment, proliferative vitreoretinopathy, and chorioretinal atrophy. Cryotherapy can be used 2–3 hours before chemotherapy administration, and that can increase the permeability of blood retinal barrier and increase the effect of chemotherapy [61, 63].

10. Chemotherapy

Chemotherapy is considered as one of the most important modalities used to treat retinoblastoma. It has been used as a main therapeutic modality achieving tumor control in up to 78% with the elimination of the need for enucleation as well as EBRT and its risk of developing second new cancers [64]. Chemotherapeutic agents can be delivered via four main routes which are intravenous chemotherapy, intra-arterial chemotherapy (IAC), intravitreal chemotherapy, and periocular chemotherapy. The most common chemotherapeutic agents used are vincristine, etoposide, and carboplatin. This (VEC) regimen is the most popular combination preferred by many experts, and this stems from its proven effect on neuronal tumors in the pediatric age group as well as its good penetration into the eye [65]. Melphalan is considered as the best and most effective agent in intra-arterial chemotherapy, and it is the most commonly used [66]. Tumor control, chemoreduction, and outcome differ from one modality and route of administration to another. Outcome also depends on the ICRB where chemotherapy can be successful in 100% in group A and it drops as low as 50% in groups D and E. Visual outcome can be maintained with a visual acuity of 6/60 or better in around two-thirds of patients [16, 67]. Adverse effects of chemotherapy observed are different from one modality to another. For instance, common side effects seen with systemic chemotherapy include transient pancytopenia, fever, and alopecia. Intra-arterial chemotherapy complications are attributed either to the procedure itself or to the chemotherapeutic agent. It can result in endovascular complications, allergy, and hematoma at the site of entry. IAC can also result in ocular vascular complications. Neutropenia is another important complication noted in IAC. Among the most frequent side effects of intravitreal chemotherapy are retinal pigment epithelium changes, iris depigmentation and atrophy, chorioretinal atrophy with vitreous hemorrhage, and retinal detachment. Fortunately, second primary malignancy

risk in chemotherapy is almost eliminated compared to EBRT which has made chemotherapy more superior in treating retinoblastoma [68–75]. A more detailed information is mentioned in the chapter entitled Retinoblastoma Management: Advances in Chemotherapy.

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Conflict of interest

There is no financial interest to disclose.

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