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Review

A Narrative Review - Therapy Options and Therapy Failure in Retinoblastoma

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Key Words
Retinoblastoma • Therapy • Therapy failure • Enucleation • Metastasis

Abstract
Retinoblastoma (RB) management has evolved over the last three decades. Goals of modern RB treatment are first to protect life and prevent metastatic disease, then preservation of the globe and useful vision. With modern treatment protocols and early disease detection success rates can reach up to 100% of disease-free-globe and eye preservation. Treatment of advanced cases remains complex, requiring aggressive chemotherapy or/and external beam radiation. Treatment protocols are extremely diverse and dependent on local resources thus success rates are variable. Here we review narratively current treatment protocols and failure rates based on a PubMed search using keywords of retinoblastoma, retinoblastoma seed, retinoblastoma treatment, enucleation.

Introduction

Retinoblastoma (RB) is the most common ocular malignancy in childhood and is lethal if untreated. Modern treatment protocols have evolved in the last three decades resulting in substantially improved treatment with up to almost a high percentage of disease-free, globe-salvaging survival rate when disease is identified in its still intraocular stage [1-5]. Goals of modern treatment aim to protect life by preventing metastatic disease, followed by globe preservation, and when possible preservation of useful vision. Advanced treatment algorithms aim for additional improvement in globe preservation even in advanced cases and are possible only in centers that can provide comprehensive treatment.

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Chemoreduction and focal treatment methods are not uniformly successful in controlling intraocular RB. Chemoreduction failure has been defined as unresponsive or recurrent RB. Local recurrence can occur at three anatomic locations: as retinal tumor, as vitreous seeds, and as subretinal seeds. Eyes that fail chemoreduction eventually require external beam radiotherapy (EBR) which can induce secondary central nervous system malignancy. Delayed diagnosis and treatment may also lead to extraocular metastasis, with central nervous system involvement having particularly poor prognosis [6, 7]. As therapy protocols are extremely diverse and vary a lot depending on region and available resources, the objective of this review is to describe current treatment protocols with respect to their success rate and causes of therapy failure in RB.

Study selection and data extraction

For this narrative review, we performed a search on Medline and PubMed using the key words: Retinoblastoma, retinoblastoma seed, retinoblastoma treatment, "retinoblastoma and enucleation". Titles and abstracts of identified studies were independently reviewed by two investigators (AC and VK) and a full-text review was carried out on potentially eligible studies to evaluate inclusion. The following data were collected: publication year, study design, diagnosis of RB, type of RB, treatment, follow-up, visual and anatomic outcomes, adverse events. Visual outcome was reported as best corrected visual acuity (BCVA) change. Anatomic outcome included the type and extension of RB, laterality and type of recurrence, incidence, and localization of recurrence. When a study provided only individual patient data because of a case series design, means were calculated. The searches yielded a total of 8853 records which were screened for eligibility. 146 articles received full-text evaluation and inclusion in the analysis. Among the 146 included studies, 12 reported general findings on classification, incidence, and mortality. The rest reported on different RB treatments.

Incidence of retinoblastoma

RB is the most common pediatric primary intraocular malignancy with an incidence of approximately 1 in 15,000 to 1 in 23,000 live births [8]. It represents 3% of childhood cancers [9]. Unilateral cases are usually diagnosed at an average age of 18 months, bilateral cases slightly earlier at an average age of about 12 months. Most of newly diagnosed cases (94%) are sporadic and only 6% are familial. There is no apparent predisposition for race, sex, or laterality. Most of RBs are unilateral; 25–35% of cases demonstrate bilateral involvement. In rare instances, the tumor is first recognized at birth, in the teens, or even in adulthood [10].

Despite the ongoing, advanced globe sparing therapies, modern literature lacks information on incidence of metastases and metastatic deaths from RB. In USA for example survival rates have increased following improved therapies from the 1970s to 2010, with 5-year overall survival reported as 93.7% for 1975–1979 up to 97% presently [11]. A large retrospective study in 2019 for unilateral RB reported an overall metastatic rate of 3.9% and death rate of 1.75% [12]. A similar UK retrospective study from 2009 reported survival rates for unilateral cases at 93% at 1 year and 86% at 20 years and for bilateral RB 86% at 1 year and 80% at 20 years [13]. Furthermore, in 2019 a large registry study reported an overall survival rate of 95.2 [14].

Table 1. Treatment option for intraocular retinoblastoma

Treatment modality	Indication
Focal treatment	
Laser Photocoagulation	< 2mm, posterior to equator
Thermotherapy	< 3mm, posterior pole/mid-periphery, no vitreous seeds
Cryotherapy	< 2mm, < 1.5 mm thickness, equator, /periphery
Enucleation	
Primary	Group e or D with no salvageable vision
Secondary	1. Failure of conservative treatment, 2. Following neoadjuvant chemotherapy for stage 3
Chemotherapy	
Neoadjuvant	Extraocular retinoblastoma
Adjuvant	Trans-scleral disease, involvement of cut-end optic nerve, extraocular disease
Chemoprophylaxis	Invasion of anterior chamber, iris, ciliary body, sclera, postlaminar optic nerve, massive choroidal involvement
Periocular	Group C and D disease
Radiotherapy	
Plaque radiotherapy	≤15 mm in diameter, ≤ 7-8 mm thick, localized vitreous invasion over the tumor, peripheral tumors
External beam radiotherapy	Stage 2 and 3 disease, metastatic sites in stage 4

Therapy of retinoblastoma

Management of RB is in constant evolution and treatment varies among different centers worldwide but highest success rates are reported from centers that can provide comprehensive therapy.

Systemic chemotherapy combined with adjunctive local treatment such as laser photocoagulation, transpupillary thermotherapy, cryotherapy, and brachytherapy has been widely used in the treatment of RB. The most common regimen for systemic chemotherapy is vincristine, carboplatin, and etoposide (VEC regimen). The ophthalmic artery infusion chemotherapy technique has been introduced to provide a targeted therapy with better tissue response while minimizing systemic toxicity and has been refined and is now known as direct intra-arterial chemotherapy (IAC) for treating advanced intraocular RB [15, 16]. A commonly used drug in IAC is melphalan with or without the combination of topotecan and/or carboplatin [17]. Intravitreal chemotherapy injection (IViC) is a further option for targeted localized treatment and has been mainly reported for treating severe and monocular cases with recurrent RB and extensive vitreous seeding [18]. Vitreous seeds represent a challenge in the management of RB because the avascular vitreous cavity has poor penetration of systemic chemotherapy. Even with IAC, approximately 30% of eyes are removed because of the presence of vitreous seeds [19, 20]. All treatment options have been summarized in Table 1.

Intra-arterial chemotherapy

Since 2008, treatment of children with RB by selective ophthalmic artery chemotherapy, IAC, has become the first-line treatment for advanced and recurrent intra-ocular RB, significantly reducing the need for enucleation and minimizing systemic chemotherapy toxicity [16, 21-23]. Specialized centers offer IAC for RB [24]; however, the worldwide use of primary IAC in advanced RB ranges from 0% to 100% with some centers enucleating 100% of 'D' eyes, while others treat 100% of 'D' eyes [25]. A retrospective analysis of 73 patients demonstrated that IAC is an effective and safe treatment for RB, with a technical

success rate of 98.5% and an overall ocular preservation rate of 78.5%. Although some patients experienced minor side effects, major complications did not occur [26]. In another retrospective study, globe salvage was achieved in 72% of primary-treated patients and in 62% of secondary-treated patients [24]. Only advanced Group D or E cases were treated in this way with an attempt to salvage the eye and minimize risk of metastatic disease, which did not occur in any of the treated cases. Complete control was achieved in 80% of the cases with recurrent solid tumor, in 55% with recurrent subretinal seeds, and in 43% with recurrent vitreous seeds [27]. Similar results with IAC were reported in a study with fewer patients; globe salvage was achieved in 72% of primary-treated cases and in 62% of secondary-treated cases with a mean follow-up of 19 months [28]. Specifically, primary therapy achieved globe salvage for group B (100%), group C (100%), group D (94%), and group E (36%) [24]. Salvation of two-thirds of eyes with advanced intra-ocular RB managed primarily with IAC without need for enucleation or external beam radiotherapy has been reported [25]. More orbital recurrences in a group primarily treated with enucleation (7.9%) than in the IAC group (1.3%) were reported in a single-institution retrospective study of advanced intraocular RB[29].

Combined intra-arterial chemotherapy and intravitreal chemotherapy

While IAC is effective for the majority of group B, C, and D eyes, the efficacy of IAC alone is limited in eyes with extensive vitreous seeds [20, 24, 30-35]. The addition of adjuvant (IViC) has been found to be effective for eyes with vitreous seeds to achieve comparable globe salvage rates for group D and E eyes with persistent active vitreous seeds [36-42]. With IViC group E eyes have improved significantly to 73% compared to 25% in the era of IAC alone [35]. Combined treatment has been reported to be effective and safe for the treatment of advanced unilateral RB achieving a high control of both the retinal tumor and vitreous seeds, particularly cloud vitreous seeds, with only one recurrent case after the initial treatment; globe salvage rate was in 93.3% with no severe systemic complications occurring and no extraocular tumor extension or metastasis during the follow-up period [43].

Combined intra-arterial chemotherapy and intravenous chemotherapy

Intravenous chemotherapy (IVC) in the treatment of RB was first used in the mid-90s and unexpectedly achieved a globe salvage rate of >90% for eyes in groups A–C [44-47]. Additionally, there is evidence that IVC as adjuvant postoperative treatment can effectively prevent metastasis in high-risk patients who have undergone enucleation [48]. However, a major obstacle to the use of IVC is the blood–retina barrier, which limits the entry of chemotherapeutic agents into the eye, reducing their efficacy while causing systemic adverse effects. Since 2006, IAC has become a common treatment method for managing RB due to its targeted application and higher local efficacy with lower overall systemic sideeffects [15, 49]. This modality has been shown to control relatively advanced tumors that would previously have required enucleation or would have failed the first-line treatment [3, 19, 20, 24-26, 32]. No additional effect of IVC combined with IAC was demonstrated in a study follow-up period of 3-year in comparison to primary IAC for treating advanced intraocular RB [50].

A study of the effectiveness of IAC, IVC and their combination in the management of group D RB demonstrated that in group D patients, primary IAC achieved ocular survival in 76.7% of eyes with less need for local consolidation treatment, whereas following primary IVC, ocular survival was 43.2% [51].

Intra-arterial chemotherapy in advanced stages

IAC improved ocular survival rates for eyes with advanced RB (naive or not) saving the majority of eyes with advanced RB in a 9-year period study [52]. 46% of advanced eyes in preverbal children treated with IAC achieved "fair" to "excellent" ERG amplitudes at last follow-up but future research is needed to determine the actual vision functional gains in this population [34].

Primary enucleation

Enucleation has been performed for RB for more than 200 years [53, 54]. Survival after enucleation for RB was 5% in 1869, 17% in 1897 and 57% in 1916 [12]. Further advances allowed some unilateral RB to be managed without primary enucleation with survival rates of 63% and 70%, and finally 92% by the end of the 20th century [55-57]. Eventually, advanced globe sparing therapies allowed some unilateral eyes to be salvaged, often with useful vision and without compromising patient survival [52]. Enucleation is still performed in every RB center worldwide but there has been a lack of recent literature on incidence of metastases and metastatic deaths following enucleation surgery. Primary enucleation for unilateral RB is still associated with a 3.9% chance of metastases within a year, mostly in patients with higher risk histopathology [12].

In a single-institution retrospective study, advanced intraocular RB primarily treated with enucleation had more frequent orbital recurrences [58]. IAC for advanced intraocular RB was not found to increase the chance of orbital recurrence, metastatic disease, or death compared with primary enucleation [29].

Berry et al. studied the risk of metastasis and orbital recurrence in advanced RB eyes treated with systemic chemoreduction versus primary enucleation and reported for both incidence of orbital recurrence and metastatic disease <1%. Globe salvage therapy with systemic chemoreduction and subsequent enucleation for poor response does not increase the risk of metastatic disease or orbital recurrence [59].

Primary intravenous chemotherapy (IVC) in combination with further treatment

For unilateral RB, IAC provided significantly superior globe salvage rate compared to IVC for group D eyes and provided significantly superior control for solid tumor, subretinal seeds, and vitreous seeds [60]. For particular locations such as macular RBs IVC plus adjuvant foveal-sparing thermotherapy provides tumor control of 83% by 4 years, and this appears to be better than IVC alone, which provides control of 65% by 4 years [61]. Tumors most destined for recurrence are small tumors [61]. The management of group E RB can be particularly difficult. For unilateral E RB or when the opposite eye has minimal tumor, enucleation with salvation of the partner eye with potential vision should be sought [44, 62]. Options for management in these cases include IVC, EBR, or a combination IVC and EBR [63]. Importantly group E RB managed with IVC and EBR showed significantly less need for enucleation or therapeutic radiotherapy than eyes treated with IVC alone. These findings merit further study [63, 64]. Furthermore, chemotherapy in group E eyes before enucleation performed more than 3 months after diagnosis possibly masks evidence of extraocular extension, increasing the risk of metastatic death from reduced surveillance of high-risk disease [65]. Currently, EBR is rarely performed, as retrospective analysis has shown a higher rate of secondary CNS malignancies after this treatment.

Intra-arterial chemotherapy as secondary therapy

IAC, as mentioned earlier, was initially developed as first-line therapy for the treatment of unilateral advanced RB but is also used as second-line therapy for relapsed RB [15, 27]. In a retrospective study, globe salvage was achieved in 72% of primary-treated patients and in 62% of secondary-treated patients [24]. Further studies have demonstrated that globe salvage rate is higher (93.3%) when IAC is used as primary therapy than when it is used as secondary therapy (79%), which is consistent with previous reports [32, 66]. IAC globe salvage is lower in patients previously treated with IVC, especially previous failed treatment as most RBs showed an initial response to intravenous chemotherapy but eventually progressed [32, 66]. This could be partially explained by multidrug resistance observed in some studies [67, 68].

Advanced D or E eyes treated with primary IVC had no metastasis in a 2 year follow up period. However, in these cases, recurrence made the secondary use of IAC necessary and complete control was achieved in 80% of the recurrent solid tumor cohort, in 55% with recurrent subretinal seeds, and in 43% with recurrent vitreous seeds [27].

Another study suggests that IAC, whether primary or secondary, is effective and fairly safe for the management of advanced RB in infants aged < 3 months; however, adverse events related to intra-arterial injection were reported and the visual outcomes cannot be neglected and require further investigation [69].

A report of the efficacy of a second course of IAC noted a 24-month ocular survival at 83% and progression-free survival at 26% [70]. Consequently, such eyes are still ‘‘at risk’’ for tumor progression even after the second round of IAC as 74% of patients demonstrated vitreous seeding requiring treatment. In other series, tumor control was achieved in 9 of 12 eyes (75%), with tumor progression requiring treatment in 5 (42%) using intravitreal melphalan for vitreous seeding and cryotherapy with or without plaque radiotherapy for subretinal seeding. Such cases warrant a close monitoring and focal therapy when appropriate [42, 71, 72].

Comparison between intra-arterial chemotherapy and intravenous chemotherapy

IVC was compared to IAC for unilateral RB and IAC was found to provide significantly superior globe salvage for group D eyes as well as superior control for solid tumor, subretinal seeds, and vitreous seeds [60].

Similar results have been reported with globe retention at 100% when IAC was the first-line therapy compared with 57% in the IVC group [73]. No metastases or deaths occurred in either group. IAC was associated with fewer side effects, faster response rates, fewer relapses, and better visual acuity than IVC treatment. There were differences between the two groups with respect to the consolidating treatments used and differences in the time frame due to availability of IVC. Despite this, the results suggest that eyes treated with first line IAC will have shorter treatment period, better ocular survival, and visual acuity than first line-treatment with IVC [73].

Comparison between intra-arterial chemotherapy and enucleation

Eyes treated initially with IAC have been shown to have ocular event-free survival rates at 2 years of greater than 80% despite their advanced stage [32]. These findings have been replicated at multiple centers, demonstrating that IAC as a primary therapy or with intravenous chemotherapy as a bridge may achieve globe salvage and tumor control in a high percentage of eyes with group D and E RB [24, 32, 74, 75]. IAC also has been shown to be useful in the treatment of vitreous seeds and to prevent development of new intraocular tumors, suggesting that it may treat ophthalmoscopically undetectable tumors present at initial diagnosis [19, 76].

While the multiple benefits and favorable risk profile of IAC have been documented in the literature, the incidence of orbital recurrence in patients treated with this modality was described in a single-institution retrospective study of advanced intraocular RB; there were more orbital recurrences in the group primarily treated with enucleation than with IAC. On the other hand, ophthalmic artery intra-arterial chemotherapy for advanced intraocular RB was not found to increase the chance of orbital recurrence, metastatic disease, or death compared with primary enucleation [58].

Focal therapy options

The use of thermal energy in conjunction with systemic chemotherapy has been shown to be synergistic [77-79]. In a transgenic murine RB cell line, the cytocidal interaction of heat and carboplatin were found to be superior to each of the monotherapies [80]. Laser treatment alone for small tumors, and combined with cryotherapy and chemotherapy for larger tumors, is effective in the treatment of RB. Complications of focal therapy can most often be avoided by using the minimal effective laser power.

Intravitreal chemotherapy

The use of IViC has reported to have a salvage rate of 51% [81]; however, unstable chromosomes in RB cells have high mitotic index, causing them to infiltrate rapidly in neighboring accessible tissue (vitreous, subretinal space, anterior chamber) which has been a concern [82, 83]. Intravitreal chemotherapy gained greater acceptance when an anti-reflux technique with needle track sterilization was introduced so there is minimal chance of extraocular spreading of tumor cells and very promising outcomes in globe salvage with advanced disease [84].

So far intravitreal therapy has been extensively tested and compared to other therapies. Intravitreal melphalan appears to be promising for group D RB with resistant vitreous seeds [85].

The management of vitreous seeds and subretinal seeds is problematic with respect to final prognosis and eye salvage [86, 87]. Salvage rates vary from 100% for group A eyes, 96% for group B eyes, 90% for group C eyes, and 48% for group D eyes [44]. The lower rate for group D eyes is usually due to active vitreous seeding [47]. Chemotherapy cannot reach therapeutic vitreous levels making treatment of vitreous seeds a challenge [88]. Intravitreal thiotepa, melphalan, and methotrexate have been used for RB [89, 90]. Melphalan was the most efficient drug among 12 tested *in vitro* and structurally nontoxic to the retina *in vivo* [90]. Therefore, intravitreal melphalan has emerged as a treatment for active vitreous seeds with considerable success [71, 91].

Treating vitreous seed clouds with IAC and intravitreous/periocular chemotherapy has resulted in a shorter regression time compared with IAC alone, fewer recurrences, fewer retreatments, and fewer enucleations [92]. The salvage rate for Group D eyes was 75% with intravitreal melphalan reaching ocular salvage in 42% over 6 years; systemic chemoreduction combined with intravitreal melphalan for seeding demonstrated a high overall salvage rate for Group D eyes in this cohort [39].

Intravitreal chemotherapy-assisted endoresection appears to be a safe and effective globe-salvaging method for refractory D RBs and may be a promising alternative to enucleation for those unresponsive to standard therapies, especially for monocular RB patients [93]. This surgical technique has to further be tested to see if extraocular metastasis occurs.

Sub-Tenon's chemotherapy

Studies have also more convenient routes of local chemotherapy such as sub-tenon's injections as an alternative to intravitreal administration. Experimental work has already demonstrated that periocular carboplatin quickly enters the vitreous reaching high concentrations, recommended for the management of Group C and Group D eyes [94]. Carboplatin sub-tenon treatment for RB with secondary vitreous seeds is safe and can salvage 30.3% of eyes without EBR with no statistically significant difference to eyes treated with intravitreal melphalan [95].

External beam radiotherapy (EBR)

EBR since 1954 was first eye salvage therapy for advanced intraocular RB and was used extensively as primary treatment [96]. Although quite effective in controlling tumor growth, enucleation was ultimately needed due to radiation complications. Further, there was also a lifelong increased risk of secondary malignancies in children with genetic predisposition (e.g. germline RB1 gene mutation) and cosmetic problems from orbital bone growth retardation [97, 98]. Consequently, EBR was successively replaced by systemic chemotherapy combined with focal therapy and reserved as a salvage option for treatment failures [99]. However, the presence of vitreous seeds, stage migration during the course of chemotherapy, as well as good vision in the other eye may not justify the risk profile of EBR [5, 100, 101].

Given the high radiation sensitivity of RB, proton beam therapy (PBT) could be a valuable rescue therapy to preserve a RB eye with a visual function in otherwise treatment resistant RB cases. PBT has distinct advantages over photon radiation therapy reducing collateral tissue damage but is not itself complications free [102, 103]. An eye preservation rate up to 90% has been demonstrated with a fairly good survival rate and low in-field recurrences even after 8 years of follow-up [104]. A lifelong risk of subsequent primary tumors cannot be excluded thus consistent monitoring is warranted.

Secondary enucleation with high dose intravenous chemotherapy

Eyes that fail chemoreduction therapy eventually require EBR and/or enucleation. Compared with Reese-Ellsworth classification (Table 2) groups I to IV, group V disease requires more often external beam radiotherapy and enucleation after chemoreduction [5, 105]. Chemoreduction failure was defined as unresponsive or recurrent disease. Unresponsive disease in 10 of 105 (9.5%) study eyes was treated with enucleation after the second chemoreduction treatment [5]. Careful handling and interpretation of histopathology of eyes with RB is necessary to assign metastatic risk [106]. Eyes with less than 3 mm choroidal invasion and without prelaminar/laminar optic nerve invasion show no recurrence and may warrant no adjuvant chemotherapy [106]. In contrast, greater than 3 mm peripapillary choroidal invasion with 1.5 mm or greater of post laminar optic nerve invasion have the poorest outcomes, supporting the need for a more intensive adjuvant chemotherapy regimen. Strict criteria for adjuvant therapy may improve outcomes of children who undergo enucleation at

Table 2. Reese-Ellsworth classification [105]

Group	Criteria
Group I (very favorable)	a) Solitary tumor, <4 DD in size, at or behind the equator b) Multiple tumors, none >4 DD in size, all at or behind the equator
Group II (favorable)	a) Solitary tumor, 4-10 DD in size, at or behind the equator b) Multiple tumors, 4-10 DD in size, behind the equator
Group III (doubtful)	a) Any lesion anterior to the equator b) Solitary tumor, >10 DD, behind the equator
Group IV (unfavorable)	a) Multiple tumors, some >10DD b) Any lesion extending anteriorly to the ora serrata
Group IV (very unfavorable)	a) Massive tumor involving over half the retina b) Vitreous seeding

diagnosis and may avoid unnecessary adjuvant chemotherapy for those who are not at risk for recurrence [106].

Treatment failure rate

Ravindran et al. reported in a big review study an enucleation rate of 32% after intra-arterial chemotherapy [107]. The rates of new tumor development/recurrences following all types of treatment have ranged from 6% to 45% [108-112]. The rate of tumor recurrence following IVC without focal treatment ranges from 35% to 45%, while the rate following chemoreduction with consolidative treatment has been lower at 17% to 18% [61, 111]. Recurrence after IAC, with consolidation, has been reported as low as 0% to 23% [16, 24, 32]. The results suggest that IAC has advantages in eyes with advanced disease, including groups D, IV, and V, but not in groups A-C, E, and I-III eyes. And although the studies cannot be directly compared due to different study design the overall success rate is higher in IAC compared to IVC and there seems to be no significant difference with respect to tumor recurrence and metastasis disease [50].

International Intraocular Retinoblastoma Classification and Intraocular Classification of Retinoblastoma Classification

When intravenous chemotherapy for intraocular RB was introduced in the 1990s, a new precise classification scheme for staging RB was adopted, the International Intraocular RB Classification (IIRC) [47]. Subsequently it has been modified as the Intraocular Classification of RB (ICRB) with refined definitions of the advanced groups D and E and has been found to successfully predict the outcome of intravenous chemotherapy (Table 3) [44].

Table 3. Classification system for Intraocular Retinoblastoma [44,47]

Group	International Intraocular Retinoblastoma Classification (IIRC)	Intraocular Classification of Retinoblastoma (ICRB)
Group A (very low risk)	All tumours are ≥3 mm, intraretinal, at least 3 mm from the foveola and 1.5 mm from the optic nerve. No vitreous or subretinal seeds	Retinoblastoma ≤ 3 mm (basal dimension or thickness)
Group B (low risk)	Discrete retinal tumour of any size /location. No vitreous or subretinal seeds. Subretinal fluid extending ≤5 mm from the base of the tumour is allowed.	Retinoblastoma > 3 mm (basal dimension or thickness) or • Macular location (≤3 mm to foveola) • Juxtapapillary location (≤1.5 mm to disc) • Additional subretinal fluid (≤3 mm from margin)
Group C (moderate risk)	Discrete retinal tumours of any size and location with focal vitreous or subretinal seeding. Any seeding must be local, fine, and limited so as to be theoretically treatable with a radioactive plaque. Up to one quadrant of subretinal fluid is allowed.	Retinoblastoma with: • Subretinal seeds ≤ 3 mm from tumour • Vitreous seeds ≤ 3 mm from tumour • Both subretinal and vitreous seeds ≤ 3 mm from tumour
Group D (high risk)	Massive, non-discrete endophytic or exophytic disease with diffuse vitreous or subretinal seeding. Retinal detachment >1 quadrant. May show 'greasy' vitreous seeding or avascular masses. Subretinal seeding may be plaque like.	Retinoblastoma with: • Subretinal seeds > 3 mm from tumour • Vitreous seeds > 3 mm from tumour • Both subretinal and vitreous seeds > 3 mm from retinoblastoma
Group E (very high risk)	Very extensive disease with eyes destruction (anatomically, functionally) with one or more of the following: Irreversible neovascular glaucoma, massive intraocular haemorrhage, aseptic orbital cellulitis, tumour anterior to anterior vitreous face, tumour touching the lens, diffuse infiltrating retinoblastoma and phthisis or pre-phthisis	Extensive retinoblastoma occupying >50% of globe or with: • Neovascular glaucoma • Opaque media from haemorrhage in anterior chamber, vitreous or subretinal space • Invasion of postlaminar optic nerve • choroid (>2 mm), sclera, orbit, anterior chamber

Risk factors of unfavorable outcome

Chemoreduction failure is defined as a treatment unresponsive or recurrent RB. Risk factors associated with low tumor response and increased need for enucleation include older age at diagnosis, greater tumor thickness, presence of vitreous seeds, subretinal fluid at baseline and retinal tumor recurrence after chemoreduction [5]. Low-income level was found to be an independent, significant predictive factor for advanced disease [1]. Extraocular/transscleral tumor extension with orbital tissue involvement as well as presence of tumor at the optic nerve represent high-risk features for recurrence [1, 113, 114]. Although anterior segment involvement has been considered a high-risk feature, recent retrospective data suggest no further treatment necessity for this [115]. Specifically, compared with high-income countries (HIC), RB patients from low-income countries had a 10.3-fold risk and 9.3-fold mortality and a 2.2-fold risk and 1.6-fold risk for local treatment failure respectively [116]. Histopathologic analysis of enucleated eyes from low to medium income countries (LMIC) and upper to middle income countries (UMIC) revealed that patients with high-risk histopathology (pT3 and pT4) fared worse in comparison with HIC [116].

Therapy failure in retinoblastoma

In HIC, most children with limited intraocular disease are cured by a combined chemotherapy and focal treatment regime [24] or enucleation for orbital and metastatic disease followed by pathology risk–adapted adjuvant chemotherapy [117-121]. In contrast, in LMICs, RB presents in an already advanced disease stage with ocular salvage rarely possible and patients suffering on incurable metastatic disease [122-127]. Finally, a considerable proportion of patients refuse enucleation and abandon treatment [128]. Abandonment of therapy is defined as the failure to return to treatment for 4 weeks or more [129]. Hence, most patients die at this stage if they do not undergo enucleation [126, 130]. This challenge requires multilevel approaches (both on cultural and medicolegal levels), seldomly available in LMICs, critically affecting survival [122, 130]. The Central American Association of Pediatric Oncology reported the results of its first RB study (AHOPCA I), on very advanced disease presentation with a 5-year overall survival (OS) rate of 0.48±0.04 [126]. In this cohort, 45 of 171 patients had unilateral Reese-Ellsworth classification group I disease, and 16% abandoned therapy. Over subsequent years, the participating institutions embarked on a regionwide initiative (AHOPCA II) aimed at enhancing diagnosis and establishing a risk-adapted therapy that involved group discussion of all patients. Herein, we reviewed the results of a risk-adapted approach for patients with advanced intraocular unilateral RB. The standard approach of upfront enucleation and adjuvant therapy adjusted to pathology risk factors was modified for patients who presented with buphthalmus and for those who refused upfront enucleation or were at risk of abandonment to include neoadjuvant chemotherapy and delayed enucleation. Enucleation also carries a risk of rupture, causing contamination of the orbit and increasing the risk of relapse [123, 130-134].

Therapy failure in retinoblastoma: Group D/E tumors

With external beam irradiation the treatment mainstay just 25 years ago clinicians worldwide began using systemic chemotherapy instead for intraocular RB. Success rates vary widely depending mainly on disease stage for A to C stage eyes. D stage eyes managed initially with systemic chemotherapy also vary but most fall in the 25–30% range [135-138]. More advanced E stage eyes are mostly enucleated [138, 139]. Direct comparison of salvage rates described in the literature is difficult since different versions for classification are in use.

According to the Reese-Ellsworth classification, globe salvage with chemoreduction is achieved in 93% of group I, 88% of group II, 83% of group III, 62% of group IV, and 43% of group V cases [44]. According to the more recent International Classification of Retinoblastoma, globe salvage with IVC is achieved in 100% of group A, 93% of group B, 90% of group C, and 47% of group D cases [44]. Group E was not included in these analyses because most ocular oncologists have avoided use of IVC for group E RB because of the anticipated high risk of failure. Furthermore, the previously used external beam radiation, although very effective in reducing tumor size salvaging globes and vison has been progressively abandoned due to increased rate of secondary metastasis rate, ocular complications as well as developmental abnormalities of soft tissue and bony orbit/scall in children [36, 140]. Thus, most eyes with group E RB have been managed with enucleation.

However, in the recent years direct ophthalmic artery infusion, also called ophthalmic artery chemosurgery (IAC), a technique in which chemotherapy is locally delivered to the eye by a micro-catheter and advanced from the femoral artery into the ophthalmic artery has given an new wind in the treatment of simple but also advanced cases mostly avoiding the need for enucleation or external beam irradiation or systemic chemotherapy [34]. Furthermore, the metastatic rate drops down to 1.5%, even lower than the 5% described in the current literature [34]. Shields and colleagues have also shown successful treatment results in advanced eyes. With a mean follow-up of 19 months in naïve patients the ocular survival is 94% in D eyes and 36% in E eyes [24]. In addition, Tuncer and colleagues recently reported a 62.9% 2-year ocular survival in D eyes also treated with IAC [25]. Similarly, Kiratli et al. demonstrated that group D patients, primary IAC achieved ocular survival in 76.7% of eyes, and less need for local consolidation treatments, whereas following primary IVC ocular survival was only 43.2% [51].

Munier et al. on the other hand demonstrated globe retention at 100% with IAC as first-line therapy and intravitreal chemotherapy (IViC) in 2008 with primary enucleation dropping from 56% to 5% [73]. Shields et al. also tried intravenous chemoreduction IVC followed by IAC and found that advanced RB (D and E) in which enucleation would be the alternative, primary systemic (IVC) followed by secondary focal IAC provides globe salvage in 57% of the eyes and with no metastatic event [27].

Berry et al. reported the rates of extraocular relapse for patients with advanced Group D and E RB eyes treated and followed over an approximate 20-year [59]. The eyes were grouped according to whether primary treatment was enucleation versus attempted salvage with systemic chemoreduction, and the main outcomes assessed were whether the incidence of orbital recurrence, metastatic disease, and death varied by initial treatment modality. Overall, the incidence of these outcome measures was 1% or less in both groups, which is lower than what has been reported previously in similar retrospective analyses [29, 58, 65, 141].

Finally, the option of subtenon chemotherapy has also been explored with carboplatin plus chemotherapy with carboplatin/etoposide/vincristine with only partial effectiveness in Group D and unacceptable ocular toxicities [142].

Therapy failure in retinoblastoma: optic nerve invasion

Overt metastatic spread of the tumor beyond the globe, such as post laminar optic nerve invasion, indicates a poorer prognosis [143]. Tumor in orbital tissues and at the cut end of the optic nerve following enucleation represent high-risk features for recurrence [113, 114, 144]. In such cases intensive/aggressive intervention with chemotherapy and often radiation is required [113, 145, 146]. In such advanced cases enucleation is a treatment option, with a cure rate of more than 90% [114, 147-150]. Chevez-Barrios et al. have further defined high risk criteria and need for adjunct therapy [106]. On the basis of their results, less than 3 mm choroidal and any prelaminar/laminar optic nerve invasion show no recurrence and may warrant no adjuvant chemotherapy [106]. However, the combination of extensive

involvement of both choroid and post laminar optic nerve invasion (i.e. 3 mm invasion in the peripapillary posterior choroid in combination with 1.5 mm post laminar optic nerve invasion) represent the highest risk of recurrence and have a poorer prognosis [106, 151-153]. In such cases a higher degree of vigilance and a more aggressive adjuvant treatment is warranted in this scenario. Furthermore, the overall prognosis of unilateral RB patients with intracranial segment of retrobulbar optic nerve invasion was poor [106]. In such cases chemotherapy and surgical treatment were necessary, but more attention should be paid to radiotherapy and intrathecal injection for improving prognosis [144].

Finally, bilateral RB cases remain challenging for ophthalmologists and pediatric oncologists despite new therapeutic strategies for eye preservation. Bernal-Diaz evaluated treatment outcomes in 88 consecutive patients (96 eyes) with bilateral RB who underwent eye salvage treatment at a single-center prior to chemotherapy with eye preservation, long-term tumor control, and functional visual acuity maintained in many children and adolescent RB survivors [154]. Seventy-eight eyes (81%) were salvaged, seven patients (8%) required brachytherapy and 34 patients (39%) underwent EBRT. Thirty-three of 78 preserved eyes (42%) achieved normal visual acuity. The overall survival rate was 86% after a mean follow-up of 10 years [154]. Weng et al. reported similar results with globe salvage rate at 73% for group D eyes and 44% for group E eyes with vision-preserving therapy [64].

Conclusion

RB is a mostly curable cancer if diagnosed and treated early. However, proper management of RB is complex. Eye and vision preservation is not guaranteed at all. The overall goal of RB management is to prevent the progression of the disease and the development of higher-risk pathologic factors that increase the risk of metastatic spread. Advances in treatment protocols and implementation of new technology have enabled a shift in treatment emphasis from enucleation in organ preservation. As each case is unique, treatment regimens must be carefully customized for varying disease presentations, available equipment, and regional culture or traditions.

Furthermore, toxicity of chemotherapy regardless of delivery routes is still a limiting factor, indicating the need for novel targeted drugs. Molecularly targeted drugs may be more effective and less toxic, and the effects of drugs would be potentiated by local delivery. This may not only save lives, but may also spare eye(s), some sight, and the quality of life of RB survivors.

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Disclosure Statement

The authors declare that no conflicts of interest exist.

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