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A Review of Recurrent Retinoblastoma: Children's Hospital Los Angeles Classification and Treatment Guidelines

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Introduction

Retinoblastoma (RB) tumor recurrence is a relatively common and critical concern in the immediate posttreatment follow-up period. With the increasing use of globe-salvaging treatment methods, monitoring for active, recurrent disease remains crucial to ensure favorable long-term prognoses for eye salvage as well as for survival. Systemic or intra-arterial chemotherapy with local consolidative therapies (eg, chemoreduction) has been successfully used to treat RB with favorable outcomes. The rates of new tumor development following all types of treatment have ranged from 6% to 45%.^{1–5} The rate of tumor recurrence following intravenous chemotherapy without focal therapies has been reported to be 35% to 45%,^{5,6} while the rate following chemoreduction with consolidative therapies has been lower at 17% to 18%.^{5,6} The numbers vary, as it is difficult sometimes, to ascertain the onset of new tumors from true tumor recurrences. This review is focused on recurrence of previously treated tumors rather than the onset of additional new tumors in cases with germline mutations although treatment approaches apply to both. Recurrence after intra-arterial chemotherapy, with consolidation, has been reported as 0% to 23%.^{7–10} This can be further risk stratified by Group classification with more advanced Groups having higher rates of recurrence, presumably due to larger tumor burden at diagnosis, and seeding.¹¹

Intraocular recurrent disease has been documented in the retina, vitreous, and subretinal regions. Recurrent disease is particularly challenging for clinicians, considering recurrent tumors and seeding may be more resistant to chemotherapy and radiation. Subretinal seeding is located in an anatomically inaccessible region, making it difficult for focal therapies to target these seeds. Despite the numerous reports on disease recurrences, the location of recurrent disease is not always specified in outcomes studies (rather indicating simply globe salvage or progressive disease in any form). Further, there is no classification system based on evidence-based literature to guide clinicians regarding the treatment of persistent or recurrent disease. This article aims to create a classification system for the types of recurrent disease in RB, based on reported risk factors, treatment history, and likely prognoses. In addition, a set of treatment guidelines, accepted by leading ocular oncologists specializing in RB, for various circumstances in each category will accompany the classification system to guide clinicians in determining the optimal treatment course for patients presenting with recurrent disease.

Recurrence: Retinal

The rates of new tumor development following all types of primary treatment range from 6% to 45%.^{1,3–5} Following failed treatment of RB with external beam radiotherapy (EBRT), plaque brachytherapy, cryotherapy, or photocoagulation, a study reported the average base diameter of the recurrent tumor was 7 mm with an average thickness of 3 mm. Vitreous seeding was present in 47 of 72 recurrent tumors, whereas 11 eyes had only vitreous seeding without a detectable retinal tumor.¹² The development of active recurrent vitreous seeding may occur even in eyes without evidence of an active recurrent retinal tumor, although the index of suspicion for retinal disease should remain high.

Following systemic chemoreduction, studies report the development of new retinal tumors ranging from 24% to 44%.^{3,4} These are similar to rates following treatment with EBRT. Rates of retinal tumor recurrence or persistence following primary intra-arterial chemotherapy range from 0% to 23%.^{7–10} Most new tumors will develop within 3 years after the initial diagnosis.¹ In a study of 162 eyes, the majority of retinal tumor recurrences occurred within 5 months of initiating chemoreduction when the patients were still receiving their planned 6 cycles of chemotherapy.⁴

Although there are reports of tumor recurrences after several years following treatment completion,¹³ nearly all retinal tumor recurrences will be presented by 3 years of follow-up.³ Several studies have suggested younger age, especially below 2 years, at diagnosis is predictive of new tumor development.^{1,2,4} Other reported predictive factors have included subretinal seeds at diagnosis,³ family history of RB or positive *RB1* mutation,^{1,4} tumor basal diameter > 16 mm at diagnosis,¹⁴ macular tumor location, and increased tumor thickness at diagnosis (thickness of 6 mm in eyes with recurrence compared with 3 mm in eyes without recurrence).⁵

The type of primary tumor regression pattern may also indicate the likelihood of retinal tumor recurrence. The regression pattern after external beam radiation has been classified from type 0 to 4, with this system also being used after chemotherapy. Type 0 indicates the disappearance of the tumor; type 1 indicates a completely calcified tumor, as suggested by a “cottage cheese”-type texture; type 2 indicates a noncalcified tumor, as suggested by a gray, translucent appearance (ie, fish flesh regression); type 3 indicates a partially calcified tumor; and type 4 indicates atrophy with a chorioretinal scar. The most desirable regression patterns are types 1 and 4, as both indicate inactive tumors, whereas type 2 indicates a pattern that can be difficult to discern from active tumor.⁵

Several studies have evaluated the regression patterns in relation to new retinal tumor recurrences. In eyes treated with EBRT, 13 recurrent tumors were reported, and the most common regression pattern was type 1 among the recurrent tumors. However, no relationship between the regression pattern and recurrence was noted. No tumor <6 mm experienced a recurrence, and recurrence was not documented beyond 4 years of age or beyond 40 months of follow-up following completion of EBRT.¹⁵ Another study evaluated rates of recurrent tumors in eyes following systemic chemotherapy with and without consolidative therapies.⁵ Type 4 regression was only evident in 5% of eyes treated with

chemotherapy alone, while type 4 regression was observed in 45% to 85% of eyes treated with both chemoreduction and consolidative therapies. In addition, type 2 regression was highest in the group treated only with chemotherapy. However, there were no regression patterns that correlated with an increased risk of tumor recurrence.⁵ Initial size was the main factor associated with recurrence.¹⁵ Despite the lack of evidence in the literature, most clinicians believe that the type 2 regression pattern (ie, fish flesh regression) is associated with the highest risk of retinal tumor recurrence following primary chemotherapy.

Recurrence: Vitreous Seeding

Vitreous seeding at diagnosis and during the treatment course presents a concern, as it is a risk factor for all types of recurrences. Relapse in the vitreous is also often cited as the most common reason for the loss of intraocular tumor control and need for secondary enucleation.^{3,16,17} As a result, during and after chemoreduction, patients need to be monitored for vitreous (and subretinal) seeding recurrence. In a study evaluating the treatment of 40 eyes with type 3 RB vitreous seed clouds with intra-arterial chemotherapy with and without intravitreal/periocular chemotherapy, 9 eyes showed recurrent disease following completion of primary treatment. Eight eyes with recurrence were treated only with intra-arterial chemotherapy. All 9 eyes had vitreous seeding recurrence with class 2 spheres, whereas 3 eyes also had a retinal tumor and 1 had subretinal seeding.¹⁸ In another study of 40 eyes treated with intravitreal melphalan for vitreous disease, 2 eyes required enucleation for extensive subretinal seeding.¹⁹ Another study evaluated the efficacy of intravitreal melphalan in 7 eyes with recurrent/persistent vitreous seeding, 1 eye required enucleation for tumor recurrence, despite the resolution of vitreous disease.²⁰ In 2 of 9 eyes treated with intravitreal chemotherapy for persistent vitreous seeding, enucleation was required for recurrent tumors.²¹ These findings strongly suggest that vitreous seeding recurrence may be associated with recurrences in other locations.

Studies have suggested that new cases of clinically evident vitreous seeding may be detected several years following otherwise apparently successful completion of chemoreduction. Shields et al³ demonstrated the detection of new cases of recurrent vitreous seeding at 5 years following chemoreduction. In a study of 54 eyes with vitreous seeding recurrence, the estimated rate of recurrence was 46% at 3 years and 50% at 5 years. The average time to vitreous seeding recurrence following discontinuation of chemoreduction was 2 months, suggesting the period immediately following chemoreduction is a critical period for monitoring the vitreous.³ Factors predictive of seeding recurrence included subretinal seeds at diagnosis,³ group E classification at diagnosis, and endophytic tumor.¹⁴

Control of vitreous seeding has been difficult due to its resistance to systemic chemotherapy and radiation. Intra-arterial chemotherapy may be an option, as a study showed regression of recurrent vitreous seeding in 16 of 18 eyes previously treated with intravenous chemotherapy.⁷ Another study of 76 previously treated and treatment-naïve eyes with vitreous seeding showed a 2-year ocular salvage rate of 64% in treatment-naïve eyes and 76% in previously treated eyes.¹⁷ However, no/minimal response to intra-arterial chemotherapy has also been documented.²² The use of intravitreal chemotherapy has been reported to be successful in treating both recurrent and persistent vitreous seeding with

upwards of 100% control of seeding.^{19,21,23–27} In 21 of 23 eyes with recurrent or persistent seeding treated with intravitreal melphalan, complete fragmentation, or response to treatment was observed after a median of 4 injections. Type 0 vitreous seeding regression is characterized by complete disappearance of the seeds; type I is classified by conversion of seeds into calcified residues; type II is classified by shapeless inactive residues; and type III is classified by a combination of types I and II.²⁶ Type 0 regression (complete regression of seeds) was reported in 14 eyes, type I was seen in 4 eyes, and type II or III was seen in 3 eyes. Diffuse or localized distribution of seeding was not predictive of regression patterns. However, significantly more injections were required to control diffuse seeding compared with localized seeding (6.5 vs. 3.5 injections).²⁶

The subtype of seeding may also indicate an important prognostic factor for determining response to intravitreal injections and risk of recurrence. Munier²⁸ has classified the type of vitreous seeding morphologically as dust, sphere, and cloud. In a study of 28 eyes presenting with recurrent or persistent vitreous seeding and treated with intravitreal injections, all 8 eyes with recurrent disease were found to have spherical seeds. Spherical seeds were the most likely to experience recurrence and exhibited the widest range of time to regression on the Kaplan-Meier curve analysis.²⁴ In another study evaluating seed type in eyes treated with intravitreal melphalan for persistent or recurrent vitreous seeding, spherical seeds were the most responsive to therapy, but regression followed by recurrence was the characteristic pattern of spheres. Of the 17 eyes enucleated for vitreous disease progression, neovascular glaucoma, and optic nerve invasion, spherical seeds were the most commonly found.²⁹ Francis et al³⁰ also demonstrated recurrent seeding was most likely to be spherical seeds. This resistance to therapy may be secondary to the anatomy of the spherical seed. Amram et al³¹ demonstrated both histologic subtypes of spherical seeds contain a core of viable tumor cells that are actively dispersed into the eye, which correlates with the clinical reports documenting the relationship between recurrent vitreous seeding and spherical seed type. Although the cloud type has been reported to require more injections and a longer length of time to achieve remission,^{24,30} these findings suggest the spherical type is the more aggressive form of seeding.

While not commonplace at most RB centers, there has been a recent report out of China suggesting vitrectomy with melphalan infusion may be an effective treatment for recurrent vitreous seeds.³² Further studies are required to better understand the safety of this therapy as it relates to extraocular relapse.

Recurrence: Subretinal Seeding

Subretinal seeding at diagnosis presents a particularly difficult challenge for clinicians, considering its relative resistance to chemotherapy and lack of accessibility to focal therapies. Subretinal seeding recurrence is a particular concern in eyes presenting with exophytic tumors with seeding within the subretinal fluid at diagnosis, although it can also occur in eyes with predominantly endophytic tumors. In a multivariate analysis, the age of 12 months or younger and tumor base > 15 mm at diagnosis was predictive of subretinal seed recurrence.³ A univariate analysis indicated subretinal fluid at presentation and subretinal fluid extending > 6 clock hours were predictive of subretinal seeding recurrence.³

Like vitreous seeding recurrence, the critical period for monitoring of subretinal seeding recurrence seems to be immediately following discontinuation of chemoreduction. Shields and colleagues reported an average interval of 2 months to subretinal seeding recurrence after discontinuing chemoreduction. However, the estimated rate of recurrence increased from 53% to 62% at 1 and 3 years, respectively, suggesting subretinal seeding recurrence may occur after several years.³

Salvaging eyes with subretinal seeding has been reported to be more effective with the use of intra-arterial chemotherapy. One study showed the regression of recurrent subretinal seeding in 6 of 11 eyes with intra-arterial chemotherapy in eyes previously treated with intravenous chemotherapy.³³ Another showed control of subretinal seeding in 16 of 18 eyes previously treated with chemoreduction.⁷ However, it should be expected that even eyes treated with intra-arterial chemotherapy may not be salvaged and possibly present later with subretinal seeding recurrence. In a study of 76 previously treated and treatment-naïve eyes with vitreous and/or subretinal seeding, rates of ocular salvage were analyzed after treatment with intra-arterial chemotherapy. The 2-year ocular salvage rate in treatment-naïve eyes with subretinal seeding was 83%, whereas the rate decreased to 50% in previously treated eyes.¹⁷ In a study of 30 eyes treated with secondary or tertiary intra-arterial chemotherapy for persistent or recurrent subretinal seeding, 7 eyes required enucleation for recurrent subretinal seeding.³⁴

Another potential option for treatment of subretinal seeding is intravitreal chemotherapy. While intended as treatment for vitreous seeds, there are reports of regression of small primary retinal and subretinal tumors/seeds with this therapy likely due to the high concentration of the chemotherapy in the vitreous adjacent to the retina. In a study of 14 advanced RB eyes previously treated with intra-arterial chemoreduction and presenting with subretinal seeding recurrence, all eyes were successfully treated with intravitreal injections and laser therapy. Subretinal seeding was seen to be completely calcified or scarred in 13 eyes, and in the final eye, the questionable active subretinal disease was treated with additional laser and cryotherapy. Two eyes had recurrent subretinal seeding at 6 and 8 months, requiring additional intravitreal injections and laser therapy.³⁵

Recurrence: Anterior Segment

While anterior segment disease at diagnosis or in the setting of recurrence is generally considered an indication for enucleation, reports of intracameral melphalan for treatment of anterior segment disease have been published.³⁶ As with vitrectomy,³² further study and close clinical follow-up are required to assess the safety of this approach as part of conservative, consolidative therapy for RB.

Recurrence: Extraocular (Iatrogenic)

Intraocular procedures, including cataract surgery, glaucoma surgery, scleral buckling with/without pars plana vitrectomy, laser therapy, and biopsy, have also been associated with recurrent RB. In a study of 45 patients undergoing ocular surgery (cataract surgery, scleral buckling, pars plana vitrectomy, or a combination), 31% of patients had evidence of

recurrent RB.³⁷ Another study evaluating 6 patients with germline RB undergoing cataract surgery or repair of rhegmatogenous retinal detachment reported tumor activity in 3 cases following intraocular surgery which required further treatment.³⁸ Orbital recurrence has also been reported in familial RB treated with systemic chemotherapy and aggressive laser treatment for a recurrence over a period of 6 months.³⁹ In histologic studies of enucleated eyes undergoing biopsy, tumor cells were identified along the fine-needle aspiration biopsy tracks,⁴⁰ and reports have showed extraocular tumor extension following intraocular biopsy.⁴¹ However, the extraocular extension following intravitreal injections is considered very minimal risk with the use of precautionary safety methods. In a multicenter study of > 3500 intravitreal injections in eyes with RB, there were no extraocular tumor events with all injections performed with at least 2 presumed precautionary injection methods.⁴²

Conclusions

On the basis of these reports and cumulative clinical experience, the following guidelines (Table 1) are recommended for recurrent RB. It should be noted that as therapy guidelines evolve, these recommendations will also evolve. Further, these are general guidelines for recurrent disease (not a primary disease) and should not dictate care outside of the best judgement and competency of the treating clinician. Finally, secondary enucleation should always be a consideration when an eye has failed primary treatment and has poor visual potential, particularly for patients with unilateral RB. 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. Thus, any attempts at continued salvage of progressive or recurrent disease in RB must be done with an emphasis toward safety, including a detailed risk-benefit discussion with the parents/primary care givers, and preservation of the life of the patient should always take priority over the salvage of an eye.

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Table 1.**Recommended Guidelines for Recurrent Retinoblastoma**

Location of Recurrence	Extent of Recurrence	Recommended Guidelines
Retina	<3 mm with adjacent scar	1. Argon or diode laser 2. Consider cryotherapy if recurrence is peripheral
	<3 mm new tumor	1. Argon or diode laser 2. Consider cryotherapy if recurrence is peripheral 3. Increase suspicion for seeding recurrence unless the patient has a germline mutation and the tumor is peripheral
Peripheral retina	<5 mm	Cryotherapy
Posterior retina	> 3 mm	1. Systemic intravenous chemotherapy or IAC, combined with laser consolidation 2. Consider secondary enucleation for unilateral eyes with poor vision or bilateral eyes with a relatively stable tumor in the contralateral eye 3. In some tumors slightly > 3 mm, aggressive laser therapy every 2–3 wk can be effective (proceed with caution as the risk of orbital relapse has been reported with aggressive laser therapy) 4. Plaque brachytherapy (ruthenium or iodine) if no active seeding is present 5. Rarely (generally reserved for an only remaining eye), EBRT may be considered in the setting of recurrence with seeding in the last remaining eye (plaque combined with IVM for vitreous seeding may also be effective)
Vitreous seeding	Clinically visible	1. IVM 2. Consider close monitoring if no signs of activity
	Clinically visible and associated with > 5 small new preretinal tumors	Intravitreal injections combined with laser consolidation for new tumors
Subretinal seeding	> 5 small new preretinal tumors (most often from 3–9 o'clock)	1. Intravitreal injections 2. May require further intravenous chemotherapy or IAC to treat seeding source
	<5 active tumors	1. Argon or diode laser 2. OCT may be possible to confirm tumors are not preretinal (in which case, consider IVM as per above)
Loss of fundus view	> 5 active tumors	Generally in the setting of a retinal recurrence; manage as per above
	Confirmed or suspected recurrence	1. A short period of evaluation (<3 mo) to see if view clears (eg, in the setting of vitreous hemorrhage or exudative RD) 2. More intensive imaging should be done with a minimum of b-scan ultrasound (or MRI scan) 3. Maintain low threshold for enucleation with confirmatory signs of recurrence on imaging or persistent loss of view and inability to follow eye appropriately

EBRT indicates external beam radiotherapy; IAC, intra-arterial chemotherapy; IVM, intravitreal melphalan; MRI, magnetic resonance imaging; OCT, optical coherence tomography; RD, retinal detachment.