Original Article

Clinical outcome and regression patterns of retinoblastoma treated with systemic chemoreduction and focal therapy: A prospective study

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Purpose: To prospectively study the clinical outcome and regression patterns of early retinoblastoma (Groups A and B) after systemic chemotherapy and focal consolidation in Indian children. **Materials and Methods:** Group A eyes were treated with focal therapy (transpupillary thermotherapy/cryotherapy) and Group B with systemic chemoreduction and focal therapy. Outcome measures were efficacy and safety of treatment, risk factors for treatment failure, regression patterns, and factors predictive of regression patterns. **Results:** Of 119 eyes (216 tumors), 14 (11.8%) were Group A and 105 (88.2%) were Group B eyes. The mean follow-up was 22.6 months. Tumor control was achieved in 111/119 eyes (93.3% overall, 100% Group A, 92.4% Group B). Eight Group B eyes (6.7%) had treatment failure. No serious systemic side-effects were noted. Risk factors for failure included larger tumors ($P = 0.001$) and proximity to posterior pole ($P = 0.014$). Regression patterns were Type 4 (50.2%), Type 3 (31.7%), Type 1 (11.1%), and Type 2 (7%). Factors predictive of Type 4 regression were smaller tumors, anterior location, younger age; Type 3 regression was associated with larger tumors, macular location, and older age. **Conclusions:** Systemic chemoreduction and focal therapy provided effective tumor control in Indian children. Factors predictive of regression patterns included age, tumor size and its location, and the modality of treatment.

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Retinoblastoma (RB) is a potentially curable cancer and its treatment is aimed at child survival, followed by globe salvage and preservation of vision.[1] The management of this most common primary intraocular malignancy in children requires a multidisciplinary approach and depends on the stage at which the tumor is first diagnosed.[2,3] In the absence of vitreous or subretinal seeding, focal consolidation with transpupillary thermotherapy (TTT) or cryotherapy, combined with systemic chemotherapy, has been the mainstay of treatment. The majority of studies on less advanced RB have been based on the Reese-Ellsworth classification system and have reported a favorable outcome in these eyes.[4-7]

With an increase in the popularity of systemic chemotherapy as the primary modality for globe salvage, the International Classification System for intraocular RB has gained worldwide acceptance, and has been found to be a good predictor of treatment success.[2,3] In the West, Shields *et al.* used the International Classification System to study outcomes after systemic chemotherapy and focal therapy and reported success rates of 100% in Group A eyes and 93% in Group B eyes.[3] To the best of our knowledge, there is no prospective study based on the International Classification System on the clinical outcome of less advanced tumors after systemic chemoreduction and focal therapy in Indian children.

Ethnic variation in retinal pigmentation is also likely to influence tumor regression patterns observed after treatment. Various patterns of tumor regression were initially described after external beam radiotherapy (EBRT) and later on, after systemic chemotherapy in Caucasian eyes.[8,9] A recent study on regression patterns in Asian eyes has been reported from China, but it is limited by a retrospective study design.[10] Therefore, this work was planned with the primary objective of evaluating the outcomes of systemic chemoreduction and/or focal therapy in Group A and Group B RB (International Classification System)[2] in Indian children. The secondary objective was to study the various types of tumor regression patterns and analyze factors that were predictive of regression patterns.

Materials and Methods

The study was designed as a prospective study. Ethical approval was obtained from the ethics committee of our institute. Children who presented to the RB clinic of our center and underwent treatment between 2010 and 2013 were recruited. An informed consent was obtained from the parents. The criterion for inclusion was RB affected eyes that were classified as Group A or Group B, according to the International Classification System.[2] Those eyes with advanced

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RB (Groups C/D/E according to the International Classification System) were excluded from the study. Patients with a history of prior treatment for RB and parents who were unwilling for follow-up were also excluded. Demographic details were noted. Visual acuity was checked with Teller/Cardiff/Snellen's acuity chart, as applicable. Ocular examination was performed under general anesthesia for baseline evaluation. Indirect ophthalmoscopy with indentation was done to screen the eye up to the ora serrata. Tumor characteristics such as the number of tumors, location, size, and distance from the optic disc and macula were noted. RetCam (RetCam Shuttle, Clarity Medical Systems Inc., CA, USA) images were taken and B-scan ultrasonography was done at baseline examination, and thereafter, at every subsequent visit. A detailed general physical and systemic examination was carried out for all children. Baseline investigations included complete hemogram, total and differential leukocyte counts, liver function tests, and renal function tests.

The treatment protocol consisted of a combination of systemic chemoreduction and focal therapy for Group B eyes and focal therapy alone for Group A eyes. Focal therapy consisted of TTT (for tumors posterior to the equator) or cryotherapy (for tumors anterior to the equator). Under general anesthesia, TTT was delivered under wide pupillary dilatation via an indirect ophthalmoscope-mounted large spot 810 nm diode laser (Iridex OcuLight SLx Tri-Mode Machine, Iridex Corp., CA, USA). A spot size of 1.2 mm and power of 250–600 mW was used. The entire surface of the tumor was covered. The end point was a light gray color change within the tumor. Cryotherapy was applied using the triple freeze-thaw method via the transconjunctival route. Group B eyes were treated initially with systemic chemoreduction and after two chemotherapy cycles, focal therapy was started. The dosage and schedule of chemotherapy was based on a standard protocol of three-drug regimen consisting of vincristine (1.5 mg/m^2 or 0.05 mg/kg for children <36 months of age on day 0 of each cycle), carboplatin (560 mg/m^2 or 18.6 mg/kg for children <36 m on day 0 of each cycle), and etoposide (150 mg/m^2 or 5 mg/kg for children <36 m on day 0 and day 1 of each cycle). Focal therapy was administered within 48–72 h of the chemotherapy cycle. Chemotherapy cycles were repeated every 28 days until complete tumor regression was observed on ophthalmoscopic examination. Regression patterns were classified from Type 0 to Type 4, as described by Shields *et al*.[9] These included Type 0 (no visible remnant), Type 1 (completely calcified remnant), Type 2 (completely noncalcified remnant), Type 3 (partially calcified remnant), and Type 4 (atrophic chorioretinal scar). The total number of chemotherapy cycles and TTT sessions required were based on the response of tumors to therapy, as assessed by examination under anesthesia at regular intervals. A tumor that showed a progression in size, the appearance of vitreous or subretinal seeds or a relapse after initial response was considered as treatment failure, with the need for alternative therapy such as intra-arterial chemotherapy, radiotherapy, or enucleation.

Upon completion of treatment, patients were followed up at regular intervals for detailed anterior segment and fundus examination. Any adverse effect due to chemotherapy was evaluated by general physical examination and systemic examination of the child by the pediatric oncologist. Toxicity due to chemotherapy was monitored by investigations such as hemogram, complete blood count, liver function tests, renal function tests, and audiometry.

The main outcome measures of our study were the efficacy and safety of systemic chemoreduction and focal therapy. Efficacy was assessed by treatment success, defined as complete regression of the tumor based on the appearance of regression pattern, and safety was assessed by the rate of ocular and systemic complications. Risk factors associated with treatment failure were analyzed. Secondary outcome measures were types of tumor regression observed after therapy and factors predictive of regression patterns.

Statistical analysis was done using SPSS Version 16.0 (SPSS Inc., Chicago, USA). Categorical and continuous variables were analyzed by using appropriate statistical tests and significance was assigned as $P \leq 0.05$.

Results

During the study period, a total of 480 children (632 eyes) were diagnosed with RB. Of these, 113 children (119 eyes) with Group A or Group B RB were recruited. The remaining 513 eyes were excluded due to the presence of Group C/D/E disease or extraocular invasion. The treatment protocol for bilateral Group C and Group D eyes consisted of systemic chemotherapy combined with focal therapy and periocular chemotherapy. Unilateral Group D eyes were treated either with combined therapy or with enucleation. Group E eyes were treated with a primary enucleation surgery.

The clinical features at presentation are shown in Table 1. The median age at presentation was 16 months (range, 3–76 months). There were 65 (57.5%) boys and 48 (42.5%) girls. Of the 113 children (119 eyes) studied, 107 cases had Group A or Group B RB in one eye, whereas six children had bilateral

Table 1: Patient and tumor characteristics at initial presentation

Patient characteristics	
Age (months)	16 (3-76)
Gender (%)	
Male	65 (57.5)
Female	48 (42.5)
Tumor characteristics	
Unifocal eyes (%)	57 (47.9)
Multifocal eyes (%)	62 (52.1)
Number of tumors per eye (mean)	1.8±1.07 (1-6)
Number of tumors per eye (*n*)	Number of eyes (*n*, %)
One	57 (47.9)
Two	43 (36.1)
Three	9 (7.6)
Four	5 (4.2)
Five	4 (3.4)
Six	1 (0.8)
Location (%)	Number of tumors (%)
Anterior to equator	24 (11.11)
Posterior to equator	156 (72.2)
Macular	36 (16.7)

Group A or Group B disease and both eyes were included. Out of the 119 eyes, 14 eyes (11.8%) in 11 children were Group A eyes and 105 eyes (88.2%) in 102 children were group B eyes. Among Group A eyes, the status of the fellow eye was as follows: Three cases had bilateral Group A disease, two cases had a normal fellow eye, and six children had Group E disease, for which a primary enucleation was carried out. None of the children in Group A received systemic chemotherapy for the fellow eye. The status of the fellow eye among Group B cases was as follows: Group E disease in 93 cases, Group B disease in three cases and within normal limits in six cases. The fellow eyes with Group E disease were treated with a primary enucleation surgery.

A total of 216 tumors were studied in 119 eyes. The mean number of tumors per eye was 1.81 ± 1.07 (range, 1–6). In 47.9% eyes (n = 57), the tumor was unifocal, and in 52.1% eyes (n = 62), more than one tumor was noted (multifocal disease). Based on their location, tumors were sub-divided into three types - tumors located anterior to the equator, posterior to the equator and extramacular, and macular tumors. The majority of tumors were located posterior to the equator and were extramacular (72.2%), followed by macular tumors (16.7%). Only 11.1% tumors were located anterior to the equator. At baseline, the average tumor size was 4.2 mm. In Group A eyes, it was 2.2 mm, whereas, in Group B eyes, it was 8.7 mm, with a statistically significant difference (P = 0.00001) between both groups.

Treatment consisted of focal therapy (TTT/cryotherapy) alone to Group A eyes and systemic chemoreduction combined with focal therapy to Group B eyes. The mean TTT power used was 362 ± 18.6 mW. For Group A eyes, the median power was 300 mW (280–320 mW), and the median number of sessions were 2 (1–3). For Group B eyes, the median power was 425 mW (300–600 mW), and the median number of sessions was 5 (3–6). The median duration of TTT per session was 209 s (6–554), with a shorter duration for Group A eyes as compared with Group B (P = 0.0001). A statistically significant difference was also noted between both groups with respect to the TTT power and the number of sessions. Group A eyes required lower power (P = 0.0004) and fewer number of sessions (P = 0.0001) as compared to Group B eyes. The median number of chemotherapy cycles was 6 (range, 4–8).

On baseline USG, in Group A eyes, the mean tumor height was 1.3 mm and in Group B eyes, it was 3.9 mm, with a statistically significant difference between both the groups (0.002). A progressive decrease in tumor height was noted in both groups after therapy. However, macular tumors in Group B eyes showed a comparatively lesser reduction in height after treatment as compared with the extramacular tumors in Group A and Group B eyes (P = 0.014).

The mean duration of follow-up was 22.6 months (range, 12–38 months).

Tumor control [Fig. 1] was achieved in 111 of the 119 eyes (93.3%, overall, 100% Group A and 92.4% Group B eyes). Of a total of 216 tumors that were treated, 208 tumors regressed after therapy whereas eight tumors had treatment failure. The Kaplan–Meier event free estimate at 36 months was 91.3% (95% confidence interval [0.86–0.97]), an event being the need for alternative treatments such as radiotherapy, intra-arterial chemotherapy or enucleation [Fig. 2]. All the eight eyes

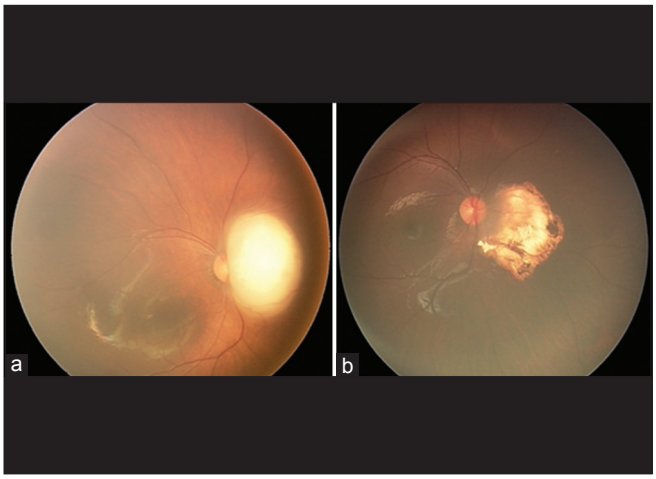

Figure 1: (a) Fundus photograph of the right eye of an 8-month-old child who presented with a Group B retinoblastoma that partially obscured the disc. (b) Posttreatment fundus photograph after transpupillary thermotherapy and six cycles of systemic chemotherapy to show regressed tumor

wherein tumor control could not be achieved with systemic chemotherapy and focal therapy were Group B eyes (8/105, 7.6%). Of these, the tumors were extramacular and posterior to the equator in five eyes, macular in two eyes, and anterior to the equator in one eye. Eyes with progressive disease showed active tumors with diffuse vitreous and subretinal seeding. Risk factors for progressive disease included larger tumors (P = 0.001) and proximity to the posterior pole (P = 0.014). The number of tumors (unifocal vs. multifocal) did not have any association with progressive disease (P = 0.392), nor did factors such as the patient's age (P = 0.872) or gender (P = 0.464).

The pretreatment median visual acuity of patients was 0.6 logMAR units, whereas the posttreatment median visual acuity was 0.5 logMAR units. Forty percent eyes had a final visual acuity better than or equal to 6/12, whereas 80% eyes had a final visual acuity better than or equal to 6/24 at last follow-up. The final visual outcome was significantly poorer in eyes with macular RB (P = 0.04), with a median final visual acuity of 6/60 in cases with macular RB, as compared to the median final visual acuity of 6/18 in extramacular tumors in Group B and Group A eyes.

The safety of treatment was assessed by the rate of ocular and systemic complications observed after therapy. None of the treated eyes developed focal iris atrophy, corneal opacities, posterior synechiae, retinal detachment, or vascular occlusion. Systemic side-effects of chemotherapy included fever, nausea, vomiting, alopecia, and loose stools, which were tackled effectively. Episodes of febrile neutropenia were recorded and managed as per standard protocol at our institute. Neutropenia was observed in 3/102 children who received systemic chemotherapy, and it was Grade 2 neutropenia (neutrophils 1000–1500/mm^3). No cases of neurotoxicity, ototoxicity, hepatotoxicity, or nephrotoxicity were encountered.

The patterns of tumor regression after treatment and factors predictive of regression patterns were also studied [Fig. 3]. Regression patterns were classified from Type 0 to Type 4, as described by Shields *et al*.[9] The most common regression pattern noted in our study was Type 4 (50.2%), followed by

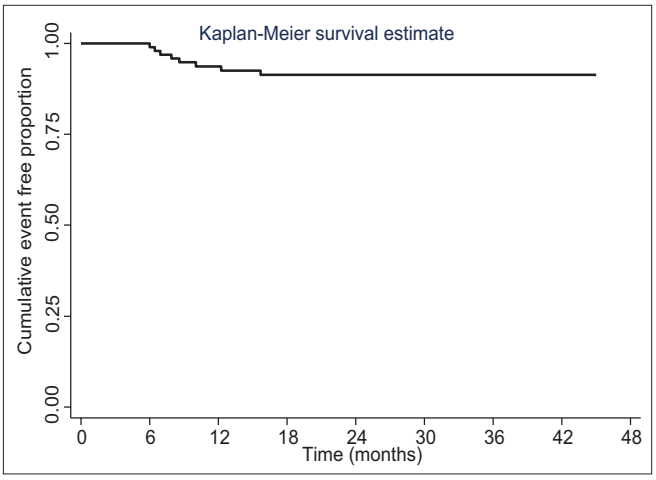

Figure 2: Kaplan–Meier event free survival

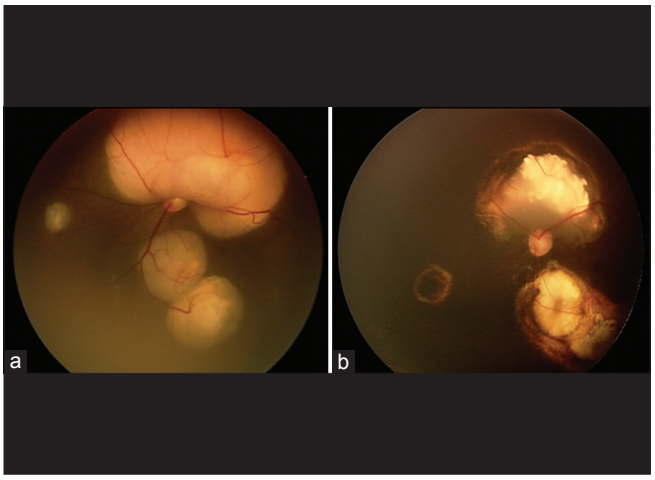

Figure 3: (a) Fundus photograph of the left eye of a 2-year-old child with multifocal active tumors. (b) Post-treatment photograph showing regressed tumours (Type 3 and Type 4 patterns)

Type 3 (31.7%), Type 1 (11.1%), and Type 2 (7%). No tumor regressed into Type 0 pattern. All Group A tumors regressed into Type 4 pattern, whereas Group B tumors most commonly regressed into Type 3 (39.6%) and Type 4 (37.8%) patterns. Any association between tumor regression pattern and tumor characteristics such as location, size, and number of tumors was studied. The results are summarized in Table 2. Univariate analysis showed a statistically significant association between regression pattern and tumor group (A vs. B, $P = 0.0001$). The location of the tumor also had a significant association with the pattern of regression ($P = 0.0001$). The predominant pattern observed in macular tumors was Type 3 (63.9%), whereas extramacular tumors located posterior or anterior to the equator regressed most frequently into a Type 4 (59.3% and 55.6%, respectively) pattern. A positive association was also noted between the regression pattern and initial tumor size ($P = 0.0001$). Tumors that had a basal diameter of < 3 mm regressed into Type 4 pattern, whereas tumors > 6 mm regressed predominantly into Type 3 pattern. The type of focal therapy (TTT vs. cryotherapy) also had a significant association with the regression pattern ($P = 0.0001$), with all tumors treated with cryotherapy regressing into flat scars. When TTT was used, the distribution was as follows: Type 4 (40.8%), Type 3 (37.4%), Type 2 (8.2%), and Type 1 (13.6%). Interestingly, the age of the child also had a significant association with the type of regression pattern seen after treatment ($P = 0.03$). Type 4 pattern was associated with younger age at presentation, whereas other regression patterns were noted in older children. On multivariate analysis, factors that were predictive of regression pattern included the age of the child, tumor size and its location, and the treatment modality.

Table 2: Association between tumor characteristics and regression patterns

Tumor characteristics	Type of regression pattern (%)				*P*
	1	2	3	4	
Tumor size (mm)					
<3	0	0	0	100	0.0001
>6	11.2	13.4	69.6	5.8	
Number					
Unifocal	9.3	11.1	46.3	33.3	0.782
Multifocal	15.0	10.0	40.0	35.0	
Location					
Anterior to equator	0	0	44.4	55.6	0.0001
Posterior to equator	12.4	6.2	22.1	59.3	
Macular	11.1	13.9	63.9	11.1	
Treatment modality					
Cryotherapy	0	0	0	100	0.0001
Transpupillary thermotherapy	13.6	8.2	37.4	40.8	

Discussion

The management of intraocular RB is complex and includes treatment options ranging from focal consolidation and systemic chemotherapy for early tumors to enucleation for advanced disease.[11] Depending upon the stage of the disease, focal therapy may be used alone or in combination with systemic chemotherapy. The majority of published studies on less advanced RB have been based on the Reese-Ellsworth classification system.[6,12,13] One such study by Friedman *et al*. reported on the effectiveness of combined chemotherapy and local therapy in avoiding EBRT and enucleation, and included 75 eyes in 47 children.[6] At a median follow-up of 13 months, the event-free survival was 74%, with 100% results in RE Groups I, II, and III.[6] In another study, Beck *et al*. reported the efficacy of two-drug chemotherapy (etoposide and carboplatin) with local treatment in preventing enucleation and EBRT.[12] In their study on 24 patients, 21 patients achieved a complete response with an event free survival of 71.4% in less advanced disease (RE Groups I–III).[12] Shields *et al*. conducted a prospective study which was based on the RE classification, and they reported success rates of 100% in Group I, 93% in Group II, and 90% in Group III when treated with combined chemotherapy and focal therapy.[13] In their study, out of 51 eyes with RE Group I–III, four eyes showed failure.[13] In contrast to these studies, our study was based on the International Classification System. We evaluated a large sample size of Group A and Group B eyes with RB (216 tumors, 119 eyes) and our results showed that 100% of Group A eyes and 92.4% of Group B eyes had a

favorable outcome. These results are comparable with the study by Shields *et al*. who first used the International Classification System to show outcomes and reported success rates of 100% for Group A eyes (*n* = 23) and 93% for Group B eyes (*n* = 96).[3] Those outcomes were reported on a patient population that was predominantly Caucasian,[3] whereas our study was conducted on Indian children. We found that treatment outcomes in our study were comparable with those reported from the West. To the best of our knowledge, there are no prospective studies on outcomes of early RB tumors on Asian eyes. The TTT power used in our study was comparatively lower. However, despite the use of lower power settings, excellent globe salvage rates were achieved. This could be attributed to better absorption of the laser due to darker pigmentation in Indian eyes.

Regarding the safety of therapy, no major systemic side-effects attributable to chemotherapy were seen in our study. Intravenous chemotherapy with VEC has been shown to be associated with minimal systemic toxicity.[14] Among ocular complications, we did not observe any significant ocular side-effects. In previous studies, Shields *et al*. have reported an incidence of 36% for focal iris atrophy and 24% for peripheral focal lens opacities.[5] Another study by Schefler *et al*. also reported an increased frequency of local complications such as iris atrophy (61%) and focal lens opacity (14%).[15] The high incidence of ocular complications observed in earlier times was associated with the use of operating microscope for TTT delivery. Unlike the indirect ophthalmoscope delivery of TTT that is used in the present era, the technique used earlier did not allow for laser angling into the eye, which resulted in a high frequency of iris atrophy with peripheral tumor treatment. With the development of indirect ophthalmoscope delivery of TTT, as was used in our study, the frequency of iris atrophy reduced significantly. Although cryotherapy-related complications have been reported in the literature, no side-effects associated with cryotherapy were seen in our cases, except for transient lid edema and conjunctival chemosis that subsided with topical medications. This could possibly be attributed to the inclusion of less advanced tumors in our study that were not associated with vitreous or subretinal seeding or retinal detachments.

We also analyzed risk factors associated with treatment failure in our study. Larger tumors and proximity to the posterior pole were predictive of treatment failure. A similar association has been reported by other investigators in previous studies.[16,17] The number of tumors (uni vs. multifocal) did not have any association with treatment outcome, which is consistent with another study that did not show any association between the number of tumors and response to therapy.[18] Shields *et al*. have previously reported an increased risk of enucleation in eyes with single tumors that were treated with chemotherapy and focal consolidation.[13]

There are very few studies on regression patterns of RB following chemotherapy. Moreover, they are limited by a retrospective design. On literature search, we found only one prospective study that has been published recently on regression patterns which was conducted on a relatively small sample size of 57 eyes (100 tumors).[19] In our study, the most common regression pattern was a flat scar (Type 4, 50.2%), followed by a mixed pattern regression (Type 3, 31.7%). In another study, Shields *et al*. have reported regression patterns as follows - Type 0 (0%), 1 (30%), 2 (3%), 3 (33%), and 4 (32%), with a comparable frequency of Type 4 and Type 3 patterns.[9] In another series of 100 RB tumors in 57 eyes of 35 patients treated with systemic chemoreduction and focal therapy, Type 3 was reported to be the predominant pattern of regression after treatment.[19] Those studies also included advanced Group C and Group D tumors, whereas our study was limited to Group A and B tumors, which could probably explain the higher proportion of flat scars (Type 4) in our patients. Interestingly, a recent study from China on 122 tumors (47 eyes) with Groups A–D RB has also reported Type 4 to be the most common pattern, with the distribution as follows: Type 0 (*n* = 3), Type 1 (*n* = 15), Type 2 (*n* = 8), Type 3 (*n* = 25), and Type 4 (*n* = 71).[10] The higher proportion of flat scars observed in our study (50% as compared to 32% in the study by Shields *et al*.) is similar to the observations on Chinese patients. This finding could also be attributed to ethnic variations in retinal pigmentation between Caucasian and Asian eyes that may influence the regression patterns observed after therapy.

In our study, tumor size and location were important factors in determining regression patterns, as has also been reported by other investigators.[9,10,19] Factors that were found to be predictive of Type 4 regression included smaller tumors, extramacular location, and younger age. Factors predictive of Type 3 and Type 1 regression included larger tumors, macular location, and older age. All Group A tumors resulted in Type 4 pattern (100%), whereas the majority of group B tumors regressed into Type 3 or Type 4 patterns. Tumors located anterior to the equator regressed into flat scars, whereas macular tumors predominantly regressed into Type 3 pattern. A similar association has been described earlier by Shields *et al*., with Type 4 pattern seen more commonly in peripheral tumors, whereas Type 3 pattern in tumors with proximity to the disc and macula.[9] In a recent study on Chinese patients, factors predictive of Type 4 regression were small tumors and anterior location, and factors predictive of Type 3 regression were older age, larger tumors, and posterior location, which is consistent with our findings.[10] Another study published recently has reported that smaller and peripheral tumors were more likely to regress into Type 4 and larger tumors and those nearer to fovea into Type 1 pattern.[19]

Regarding the chemotherapy regimen, some investigators have found a two-drug chemotherapy regimen consisting of vincristine and carboplatin to be adequate therapy for low stage RB. Etoposide is an anti-DNA topoisomerase agent that has been associated with an increased risk of secondary leukemia, specifically acute myeloid leukemia. Because of the potentially increased risk of secondary malignancies when using etoposide, a two-drug regimen consisting of vincristine and carboplatin was used in combination with focal therapy in a study by Alkofide *et al*. and found to be effective for early tumors.[20] In another study, 25 patients (43 eyes) with newly diagnosed intraocular RB received treatment with vincristine and carboplatin, combined with focal treatment.[21] The event-free survival was defined as the length of time to EBRT or enucleation. The ocular salvage rates were 83.3% for Reese- Ellsworth Group I–III eyes and 52.6% for Group IV and V eyes.[21] The authors concluded that in combination with appropriate early intensive focal treatments, chemoreduction with vincristine and carboplatin, without etoposide, may be an alternative treatment for patients with early-stage intraocular RB.[21]

To summarize, the clinical outcome and regression patterns of Group A and B RB in a large series of Indian eyes were evaluated by a prospective study. Systemic chemoreduction and focal therapy resulted in a favorable outcome, with tumor control rates comparable with the West. Our study found the standard approach of intravenous chemotherapy and focal consolidation to be effective and safe and supports its use as first-line therapy for these cases, especially as newer globe salvage modalities such as selective intra-arterial chemotherapy is still under long-term evaluation in terms of local control and systemic as well as ocular side-effects. Risk factors for failure included a large tumor size and proximity to the posterior pole. Type 4 and Type 3 patterns were the most common regression patterns observed. Factors predictive of regression pattern were age of the patient, size of the tumor and its location, and the modality of treatment.

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Conflicts of interest

There are no conflicts of interest.

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