**Primary Subretinal Seeding in Retinoblastoma: Clinical Presentation and Treatment Outcomes**

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**Running title**: Subretinal seeding in retinoblastoma

**Conflict of Interest:** There are any no competing financial interests in relation to the work described in this manuscript

**Funding source:** This work was supported by The Operation Eyesight Universal Institute for Eye Cancer and Hyderabad Eye Research Foundation, Hyderabad, India.

**Acknowledgments:** None

**Ethical Approval:** This study was conducted in accordance with the Declaration of Helsinki. The collection and evaluation of all protected patient health information was performed in a Health Insurance Portability and Accountability Act-compliant manner. This study was approved by the Institutional Review board at L V Prasad Eye Institute (Ethics Ref No LEC-BHR-R-06-22-350). A written informed consent was obtained from parent/legal guardian to participate in the study.

**Statement of Informed Consent:** Informed consent was obtained from the participants' parent/legal guardian/next of kin to participate in the study prior to performing the procedure, including permission for publication of all photographs and images included herein.

**Author contributing statement:**

KB was responsible for collecting the data, review of literature and writing the first manuscript draft. VR was responsible for designing the study, extracting and analyzing data, interpreting results, updating reference lists and critical inputs. SKG was responsible in collecting, processing and image analysis part of the study. VAR was responsible for reviewing the final manuscript and provide feedback on the draft. SK contributed to the design of the study, critically reviewing the final draft and provided feedback on the manuscript.

**Data Availability Statement:** All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

**Abstract:**

Introduction: To describe the clinical features and treatment outcomes of primary subretinal seeds (SRS) in patients with intraocular retinoblastoma (RB).

Methods: Descriptive analysis of primary SRS in 47 patients (50 eyes) with RB.

Results: Mean age was 19 months (range, 2–72 months) and 55% (n=26) of the subjects were male. At presentation, the SRS involved two or more quadrants in 88% of eyes. Most seeds appeared yellowish-grey (66%) and round to oval in shape (48%). Two-thirds of SRS were seen posterior to the equator and within 5 mm from the main tumor. Associated features included subretinal fluid in 50 eyes (100%), total retinal detachment in 28 eyes (56%) and vitreous seeds in 20 eyes (40%). Treatment included intravenous chemotherapy (IVC) (n=47; 94%), enucleation (n=2; 4%), and intra-arterial chemotherapy (n=1; 2%). SRS treatment included adjunct use of focal transpupillary thermotherapy and/or cryotherapy (n=20, 40%). Retinal tumor control was achieved in 36 eyes (76%) with 32 eyes (78%) showing a type 3 regression pattern, while SRS completely regressed in 24 (48%) eyes, partially in 15 (30%) and worsened in 2 (4%) eyes. Over a mean follow-up of 30 months (range, 3–68 months), SRS recurrence was noted in 12 eyes (29%), globe salvage was achieved in 39 eyes (78%), and one (4%) patient died of presumed metastasis.

Conclusion: Primary SRS poses a therapeutic challenge during RB treatment. SRS responds moderately to systemic IVC, with one-third cases showing SRS recurrence and one-fifth ultimately requiring enucleation.

**Keywords:** Retinoblastoma; subretinal seeding; ophthalmic oncology; chemotherapy; treatment

**Introduction**

Retinoblastoma (RB) is the most common intraocular tumor in children, accounting for approximately 11% of cancers occurring in the first year of life, with 95% diagnosed before 5 years of age.[1] In the last two decades, chemotherapy has become the mainstay of RB treatment delivered primarily through intravenous chemotherapy (IVC) and intra-arterial chemotherapy (IAC). [2-4] Tumor seeding is one of the major predictive factors for failure of both IVC and IAC.[5, 6] Intravitreal chemotherapy (iVitc) has emerged as an effective adjuvant treatment for vitreous seeding, achieving complete regression in 82%–100% eyes.[7, 8]

# Subretinal seeding constitutes an important part of RB management and poses a significant challenge. Subretinal seeding recurrence is usually reported following treatment of large-exophytic tumors (tumor base >15 mm) with primary IVC at an average interval of 2 months necessitating use of adjunctive focal treatment.[9, 10] Intra-arterial chemotherapy with its local administration of the chemotherapy close to the targeted area has reported a 2-year ocular salvage rate of 83% in treatment-naive eyes, whereas the success rate reduces to 50% in the previously treated eyes.[4] Similarly, in a study by Say et al., patients presenting with massive persistent or recurrent subretinal seeding following previous chemotherapy exposure and treated with secondary and tertiary IAC reported lasting SRS control and globe salvage in only 50% of eyes.[11] Abramson et al. have reported expanded use of intravitreal chemotherapy along with focal laser photocoagulation for SRS, achieving complete regression in more than 90% of cases.[12, 13]

At present, there are no clear guidelines or agreement among ophthalmologists regarding the diagnosis and management of SRS or its recurrence following primary chemoreduction. Depending on the primary tumor dimension, seed location, number of quadrants involved, presence of subretinal fluid (SRF) and accessibility of available resources, treatment options vary from primary IVC[5] with or without focal transpupillary thermotherapy (TTT) and primary IAC.[4, 14] Here, we analyzed the clinical presentation and treatment outcomes of primary SRS in patients with intraocular RB.

**Methods**

A retrospective chart review of all RB patients diagnosed with primary SRS were included and reviewed for final analysis. A computerized database search was conducted for the diagnosis “Retinoblastoma” from January 2017 to April 2021. The medical records of all RB patients with primary SRS were reviewed. Patients with adequate data related to clinical presentation and tumor grouping (Group C and D) at the first visit were included in the study. Exclusion criteria included patients with follow-up of less than 3 months, diagnosis of new SRS during the follow-up period, Group E or extraocular RB at first visit. This study was conducted at The Operation Eyesight Universal Institute for Eye Cancer at L V Prasad Eye Institute, Hyderabad, India. Institutional review board approval was obtained for this study.

Patients’ demographic details like age, gender, family history of RB, presenting signs, symptoms and tumor laterality were recorded. Photographic documentation was performed in all cases using a RetCam 2 wide field imaging system and all tumors were also documented with fundus drawings. Fundus drawings and RetCam images were reviewed for accurate tumor and SRS details such as location, shape, size, number, color, quadrant, distance from optic nerve, fovea and primary tumor, presence of SRF, and associated features like vitreous seeding, vitreous hemorrhage and retinal detachment. All eyes with intraocular tumors were classified based on the International Classification of Intraocular Retinoblastoma (ICRB).[15]

The details of primary treatment (transpupillary thermotherapy (TTT), cryotherapy, intravenous chemotherapy (IVC), intra-arterial chemotherapy (IAC), external beam radiotherapy, and enucleation) were recorded. All cases were managed by a single ocular oncologist (SK). As per the institute protocol, all bilateral cases were treated with a standard intravenous chemotherapeutic regimen consisting of 6-cycles of vincristine, etoposide, and carboplatin, administered every 3 weeks. All unilateral cases were offered both options of IVC and IAC, and the treatment was planned based on the parents’ choice of treatment. Focal TTT was applied at the discretion of the ophthalmologist after 1 to 2 cycles of chemotherapy to the SRS seen in the area adjoining the primary tumor or as an adjuvant treatment after the completion of 6 cycles of IVC. Laser treatment was delivered with the Iris diode laser (810 nm) (Iridex Corp., Mountain View, CA). The 1.2-mm spot size was aimed through a dilated pupil using the indirect ophthalmoscope and a 20-diopter lens. The laser was set at 300 mW initially, and then the power was increased as necessary until a gray–white appearance of the tumor was achieved.

Recurrences in the form of retinal tumor, SRS, or vitreous seeding and the treatment of such recurrences were recorded. Post-treatment, primary tumor regression patterns, and any recurrence of SRS were noted. The regression patterns were classified as type 0 (no visible residua), type I (fully calcified tumor), type II (fleshy tissue with without any calcification), type III (mixed calcific and fleshy tumor), or type IV (atrophic chorioretinal scar).[16] Partial regression of the tumor was defined as the residual area of the active tumor. SRS regression at the last follow-up was classified as complete regression (no tumor activity), partial regression (residual activity) or worsened (increase in size and extent).

The main outcome measures were primary tumor and SRS regression, globe salvage, metastasis and survival in these patients. Factors influencing the primary tumor control and SRS regression were analyzed. SPSS ver. 17.0 (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses. Statistical significance was set at *p* < 0.05.

**Results:**

Of the 676 patients diagnosed with RB during the study period, 47 patients (50 eyes) had primary SRS belonging to Group C and D at presentation (8%). The mean age at diagnosis was 19 months (median, 12 months; range, 2 to 72 months). There were 26 (55%) males and 21 (45%) females. About 55% of patients (n=26) had bilateral presentation of RB, however only 3 patients (6%) had bilateral SRS. Familial origin of RB was noted in 5 patients (11%) **(Table 1)**.

The most common presenting complaint was leukocoria (n=38; 81%) followed by strabismus (n=3, 6%) with a mean duration of symptoms of 8 weeks (median, 7 weeks; range, 0–48 weeks). Based on ICRB, 16 eyes (32%) belonged to Group C and 34 eyes (68%) to Group D. Most tumors were exophytic variant (n=38; 76%) **(Table 1)**.

Of the 50 eyes, SRS involved two or more quadrants in 44 eyes (88%), mostly located in inferior (36%) and temporal quadrants (30%). In two-thirds of eyes (64%), SRS were seen at the posterior pole located <5 mm from the primary tumor. Most seeds appeared yellowish-grey (66%), round to oval in shape (48%) with a mean size of 1.1 mm (range, 0.1–6 mm) and a total number less than 10 in 26 eyes (52%). The mean basal tumor diameter was 10 mm (median, 10 mm; range, 2.5 to 18 mm) and the mean tumor thickness was 8.5 mm (median, 9 mm; range, 3.5 to 14 mm). Associated features included subretinal fluid around the seeds (n=50; 100%), total retinal detachment (n=28, 56%), vitreous seeding (n=20; 40%), and vitreous hemorrhage (n=9, 18%) **(Table 2)**.

Of the 50 eyes, primary tumors were treated with IVC in 47 eyes (94%), primary enucleation in 2 eyes (4%), and primary IAC in 1 eye (2%). Adjunct focal treatment for SRS included TTT (n=16) and TTT with cryotherapy (n=4). Representative case illustrations are described in **Figure 1**.

At a mean follow-up period of 30 months (median, 18 months; range, 3–68 months), primary tumor completely regressed in 36 eyes (75%), partially regressed in 2 eyes (4%) and tumor worsened in 3 eyes (6%). The most common regression pattern for the retinal tumor was type 3 (32 eyes, 78%). In comparison, SRS completely regressed in 24 eyes (50%), partially regressed in 15 eyes (31%) and worsened despite treatment in 2 eyes (4%) **(Table 3)**.

Tumor recurrences were observed in 25 (52%) eyes, of which recurrence in the form of SRS was noted in 12 eyes, solid tumor alone in 11 eyes and vitreous seeding in 2 eyes. Solid tumor recurrence was treated with a repeat six cycles of IVC or three cycles of IAC. Additionally, focal SRS were treated with multiple sessions of TTT and/or cryotherapy and diffuse SRS with six cycles of IVC. Failed IVC cases were treated with secondary enucleation (n=5). Various determinants like larger tumor size (mean tumor basal dimension of 11 mm and tumor thickness of 9.5 mm), and advanced stage of disease-related factors such as total retinal detachment (64%), combined use of TTT during chemotherapy (55%) and tumors exhibiting type 3 regression (100%) contributed to imcreased risk of SRS recurrence. At the last follow-up, globe salvage rate was 78% (39 eyes) while one child died of presumed metastasis. This child had RB with extraocular extension in the right eye and Group C with focal SRS in the left eye. The child was started on six cycles of high-dose systemic IVC followed by right eye secondary enucleation. Histopathology revealed non-viable calcified tumor with no high-risk features. The child was due for external beam radiotherapy for the right eye followed by six more cycles of high-dose chemotherapy but died nine months after enucleation.

**Discussion:**

Retinoblastoma seeding is characterized by intraocular dissemination of tumor seeds within the subretinal space or vitreous compartment referred as subretinal or vitreous seeds, respectively.[17] Vitreous seeds are further classified on the basis of seeding patterns into dust, sphere, or cloud formation.[17] SRS is typically observed in advanced intraocular RB and represents a major determinant for eye grouping at presentation. Despite this, there is very limited understanding of primary SRS related to its occurrence, seed characteristics and treatment outcomes. Most studies reported in the literature are limited to SRS recurrence and its treatment outcomes.[9-11, 18] Also, the international classification of RB includes SRS as a different subcategory from vitreous seeding, while most studies assess the effect of chemotherapy based on overall grouping rather than subcategory, thus the effect of chemotherapy on SRS specifically remains unevaluated. We analyzed the clinical presentation and treatment outcome of primary SRS in patients with intraocular RB.

In our study, the mean age of presentation was 19 months (median 12 months). When, compared with our previous publication of RB including all tumors, the mean age of presentation of RB was 29 months (median 24 months),[19] implying that patients with SRS tend to present at a younger age (a minimum of 10 months earlier). Similarly, a study by Abramson et al. has reported that patients with SRS at presentation were younger (median, 18 months) and had advanced stage of disease (Group D or above in 93% of eyes).[4] Similarly, in our study, two-thirds of eyes had advanced disease (Group D) at presentation.

In our series, 38 eyes had tumor growth toward the subretinal space termed as exophytic variant. The origin and spread of active tumor cells within the subretinal space are poorly understood. Due to the discohesive property of RB cells, detached tumor cells in the presence of subretinal fluid can migrate through the subretinal space to distant areas.[20] In our study, two-thirds of eyes had SRS located at the posterior pole, less than 5 mm from the primary solid tumor and had diffuse variant involving more than two quadrants. This explains that the origin of SRS is from the primary solid tumor, which over the time breaks into small focal seeds ranging from 0.1 to 6 mm in size. The spread of tumor cells to adjacent areas (less than 5 mm) from the primary tumor is facilitated by the presence of SRF seen in 100% of cases, while the presence of exudative retinal detachment (56%) can be postulated for the spread of SRS at distant sites. Of the 50 eyes, 34 eyes (68%) belonged to Group D, suggestive of diffuse SRS involving two or more quadrants. Hand-held optical coherence tomography (HH-OCT) can be a valuable tool for differentiating small solid tumors (less than 1 mm) from SRS. This has been reported by Soliman et al. where HH-OCT was found to influence the management of RB by either confirming clinical findings (83% of OCT sessions) or changing the treatment course (17% of OCT sessions).[21] In our series, we have used fundus photographs taken using Retcam 2 to confirm the diagnosis of SRS.

Despite recent advances of use of IAC and intravitreal chemotherapy in the last decade, the treatment of advanced tumors remains a concern. Tumor seeding particularly SRS is one of the major predictive factors for failure of both IVC[5] and IAC[6] necessitating enucleation. In our series, 48% of cases were treated with systemic IVC alone while in remaining 46% adjunct focal treatment-like TTT and/or cryotherapy were administered. A total of 7 eyes (14%) underwent enucleation either as a primary (2 eyes) or a secondary procedure following failed IVC (5 eyes). A real-world outcome analysis of systemic IVC for RB patients reported local tumour control (without need for enucleation or external beam radiotherapy (EBRT)) of 91% and 71% for Group C and D, respectively, at 2 years.[22] In our series, a similar globe salvage rate of 78% was reported, while in comparison, SRS regressed completely in only half of the eyes (50%) and partially regressed in the remaining 31% of cases. This can be attributed to the avascular portion of the SRS, which responds poorly to systemic IVC compared to solid vascularized tumor.[17] Also, other factors such the location of SRS away from the primary tumor, the inability of chemotherapeutic drugs to achieve tumoricidal concentration within the subretinal space can be attributed to the poor therapeutic response to systemic IVC. More recently, the advent of intraarterial chemotherapy appears to have significantly improved the prognosis for eye preservation (70 to 80%) of group D eyes.[4, 22-24] Abramson et al. have reported 2-year success rates of IAC at 83% in RB eyes that were treatment naive and 50% in eyes that had been previously treated.[4] Intravitreal chemotherapy (iVitc), an targeted approach that delivers the highest concentration of drug in the vitreous cavity without systemic toxicity, has emerged since 2012 as an effective adjuvant treatment for vitreous seeding.[25-28] An expanded use of iVitc for treatment of SRS have been advocated in a few instances as a adjunctive therapy in globe-sparing treatment, however more pharmacokinetics studies regarding diffusion of drug from the vitreous cavity into subretinal space and achieving therapeutic concentration need to be studied.[12]

Tumor seeding in the forms of vitreous and subretinal, is a known cause of chemotherapy failure, ultimately requiring enucleation.[5] Shields and colleagues have reported SRS recurrence in 53% of eyes within 1 year after IVC and 62% after 3 years.[9] In our series, 25 eyes (61%) had tumor recurrence out of which 12 eyes (29%) had SRS recurrence at a mean duration of 2.5 months following IVC. A previous study by Shields et al. have reported an average interval of 2 months to SRS recurrence after discontinuing chemoreduction.[9] Treatment for SRS recurrence depends upon the location, focality and presence of retinal detachment. Focal SRS are usually treated with local treatment modalities, such as TTT, cryotherapy, or plaque radiotherapy; while, diffuse SRS requires repeat IVC, IAC, or enucleation.[4] In our series, focal SRS recurrence was treated with TTT (6 eyes), diffuse SRS with repeat systemic IVC (2 eyes), massive tumor and SRS recurrence with secondary enucleation (2 eyes) and IAC (1 eye). Despite good control of SRS recurrence (64%), 5 eyes ultimately required enucleation because of massive tumor and SRS recurrence (3 eyes), total retinal detachment (1 eye) and vitreous hemorrhage (1 eye).

# In our series, globe salvage rates when analyzed as per the ICRB classification showed 100% and 68% globe salvage rates for Group C and D tumors, respectively. This is comparable to previous studies reporting long-term outcomes following IVC.[3, 10, 18, 29, 30] At last follow-up, no evidence of extraocular or distant metastases was seen, however one child with orbital RB in the contralateral eye died of presumed metastasis.

This study has several limitations, including small sample size, retrospective study, lack of OCT imaging to differentiate small solid tumors from SRS and possible treatment bias. However, all cases were managed by a single ocular oncologist, thus limiting bias within the study group. Eyes with advanced stage of disease (Group E) or those with histopathological evidence of SRS were excluded from the study. Since the previous studies have analyzed treatment outcomes based on tumor grouping including SRS and vitreous seeds rather than tumor sub-grouping including SRS alone, comparison with previous studies is difficult. With the increasing availability and improved safety of IAC, future studies comparing systemic IVC with IAC for treating primary SRS would be the way forward to improve upon our practice pattern in managing such challenging cases.

In conclusion**,** primary SRS constitute an important subset of RB patients seen in our clinical practice (8%). Primary SRS poses a therapeutic challenge during RB treatment because of its specific seed characteristics and location within the subretinal space, which is unamenable to systemic intravenous chemotherapy. Systemic intravenous chemotherapy has a moderate effect on the control of SRS, with one-third cases showing SRS recurrence and one-fifth ultimately requiring enucleation. Recent advances like IAC and intravitreal chemotherapy are now becoming more popular and have shown better control of SRS and vitreous seeds, however this needs to be studied further and validated in a larger cohort.

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**Legends:**

Figure 1: Primary subretinal seeding (SRS) – characteristics and treatment reponse

(A) A 3-year-old girl presented with right eye group D exophytic retinoblastoma (RB) involving the nasal and inferior quadrants with diffuse subretinal seeding seen involving more than two quadrants. Fundus photograph showed multifocal, round, yellow seeds in the subretinal space at the posterior pole. (B) A 3-year-old boy presented with right eye group C and left eye group D RB. Fundus photograph of the right eye showed a large exophytic tumor involving the macular area with surrounding subretinal fluid and SRS seen adjacent to the tumor margin. Also, nasal to the disc there were multiple greyish, localized SRS associated with SRF. (C) A 2-year-old boy presented with right eye group D exophytic tumor involving the posterior pole with total retinal detachment. Fundus photograph showed multiple diffuse SRS observed adjacent to the tumor and complete nasal half of the retina. The child underwent six cycles of systemic intravenous chemotherapy (IVC) along with focal transpupillary thermotherapy (TTT) to SRS. (D) Post treatment, the solid tumor showed type 3 regression with partial regression of SRS. However, two months later the child present with massive SRS recurrence and enucleation was performed. (E) A 2-year-old boy presented with right eye group D exophytic RB involving the macular area with diffuse SRS involving two quadrants. There were multifocal SRSs observed in the temporal quadrant adjacent to the primary solid tumor and focal seeds in the inferior quadrant. The child underwent six cycles of systemic IVC along with focal cryotherapy and TTT to SRS. (F) Post treatment, the solid tumor showed type 3 regression with partial regression of SRS. At last follow-up after multiple sessions of TTT, SRS regressed with flat chorioretinal atrophic scars.