



Original research

# Management of retinal detachment in retinoblastoma with globe conserving treatment

Ibrahim Elaraoud<sup>a</sup>, Soon Ch'ng<sup>a</sup>, David Karl<sup>a</sup>, Dimitrios Kalogeropoulos<sup>a,b,\*</sup>,  
Randhir Chavan<sup>a</sup>, Ash Sharma<sup>a</sup>

<sup>a</sup> Birmingham and Midland Eye Centre, Birmingham, United Kingdom

<sup>b</sup> Department of Ophthalmology, Faculty of Medicine, School of Health Sciences, University of Ioannina, Ioannina, Greece

Received 30 April 2018; revised 20 August 2018; accepted 5 September 2018

Available online 22 September 2018

## Abstract

**Purpose:** To investigate the features and outcomes of retinoblastoma (Rb) patients complicated by development of retinal detachment (RD) following systemic chemotherapy with or without local focal consolidation treatment and without external beam radiotherapy (EBRT).

**Methods:** A retrospective study of all Rb patients between April 2002 and April 2012 at a tertiary hospital center (Birmingham Children's Hospital and Birmingham Midlands Eye Centre, United Kingdom). All eyes that had developed RD during or after systemic treatment with or without local focal consolidation treatment were included in the study. The time interval between the type of treatment of Rb, development of RD and relevant surgical intervention were analyzed. Patients with exudative RD were treated conservatively through observation and patients with rhegmatogenous RD were treated with scleral buckling. Final anatomical retinal reattachment rate and visual acuity outcomes were analyzed.

**Results:** A total of 258 patients were treated for Rb over the 10-year period. One hundred sixty-nine patients were managed with globe conserving treatment. Ten (5.92%) eyes of 10 patients were complicated with RD. Five eyes were exudative or presumed exudative type of RD while the other five eyes were rhegmatogenous or presumed rhegmatogenous RD. In the exudative group, two patients achieved visual acuity (VA) of 0.2 Single Kays (20/32 Snellen), and the other two patients achieved 0.85 and 0.86 Crowded Kays (20/142 and 20/145 Snellen), respectively, after the RD had resolved. The last patient in the group had to be enucleated due to tumor recurrences. The median time for the exudative RD to resolve is 15 weeks (range, 4–36 weeks). In the rhegmatogenous group, 3 of the 4 operated patients achieved retinal reattachment. The final postoperative VA ranged between 0.05 Crowded Kays to 1.84 Crowded Kays (20/22 to 20/1384 Snellen). The other patient was treated conservatively as no retinal breaks were found with previous cryotherapy and thermotherapy. The final VA in this patient was hand movement, and the RD did not reattach. The median time for the rhegmatogenous RD to reattach is 6 weeks (range, 4–8 weeks). There were no intra- and postoperative complications.

**Conclusions:** With long-term conservative management through observation, exudative Rb after systemic treatment of Rb will tend to resolve by itself. However, supplementary local treatment with cryoretinopexy or laser photocoagulation during the systemic treatment of Rb can lead to an increased risk of rhegmatogenous RD. In these cases, most rhegmatogenous RD are successfully repaired with non-drainage scleral buckling and cryoretinopexy.

Copyright © 2018, Iranian Society of Ophthalmology. Production and hosting by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

**Keywords:** Retinoblastoma; Rhegmatogenous retinal detachment; Scleral buckling; Cryoretinopexy

Disclosure of potential conflicts of interest: All authors declare that there is no conflict of interest.

Funding sources: All authors declare that they received no funding for this study.

\* Corresponding author. Birmingham and Midland Eye Centre, City Hospital NHS Trust, Dudley Rd, Birmingham, B18 7QH, United Kingdom.

E-mail address: [dkalog1990@gmail.com](mailto:dkalog1990@gmail.com) (D. Kalogeropoulos).

Peer review under responsibility of the Iranian Society of Ophthalmology.

<https://doi.org/10.1016/j.joco.2018.09.002>

2452-2325/Copyright © 2018, Iranian Society of Ophthalmology. Production and hosting by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

## Introduction

Systemic chemotherapy with focal consolidation treatment is the most preferred globe conserving treatment for retinoblastoma (Rb).<sup>1,2</sup> It has largely replaced external beam radiotherapy (EBRT) as the treatment of choice for conservative management of Rb.<sup>1,2</sup> Although the success rate of globe salvage techniques is improving, local ocular complications such as retinal detachment (RD) may complicate the Rb management at the time of diagnosis, during and after treatment.<sup>3–8</sup> Most RD cases in Rb are associated with the use of EBRT combined with other globe-conserving treatments such as systemic chemotherapy or local cryoretinopexy.<sup>3–6</sup> However, there are only a few reported studies of RD occurring during primary chemoreduction of Rb with no EBRT.<sup>3,4,7–10</sup> Therefore, the aim of our study is to assess the characteristics and outcomes of all our Rb that developed RD after the start of their systemic chemotherapy combined with or without local focal consolidation and without EBRT.

## Methods

A retrospective study of all patients treated for Rb between April 2002 and April 2012 at a tertiary hospital center (Birmingham Children's Hospital and Birmingham Midlands Eye Centre, United Kingdom) was performed. The study had approval from the local institutional review board. The study adhered to the tenets of the Declaration of Helsinki, and all patient data extracted were anonymized for analysis. All eyes with no history of exudative or rhegmatogenous RD but developed RD during or after their systemic chemotherapy treatment with or without local focal consolidation treatment were included in the study. The standard treatment in our unit comprised of primary chemoreduction treatment by three to six cycles of "JOE" chemotherapy (Vincristine, Etoposide, and Carboplatin), secondary treatment of local consolidation comprising of trans-scleral cryotherapy with or without laser thermotherapy and salvage treatment for tumor recurrences predominantly by plaque radiotherapy or intra-arterial chemotherapy (IAC) using melphalan. The general demographics and clinical characteristics of the condition were collected which includes age at diagnosis of Rb, gender, laterality of the eye involved, age of the diagnosis of Rb, status of the fellow eye, International Classification of Retinoblastoma (ICRB) on initial examination, and all globe conserving management used. The data collected for the management of the RD includes the type of RD, type of RD intervention, interval between the most recent treatment of Rb and development of RD, age of the development of the RD, time interval to complete resolution of the RD after treatment, follow-up period, postoperative retinal reattachment rate, Rb status, and final VA outcomes. Intra- and postoperative complications were also recorded. Patients with rhegmatogenous RD were treated with scleral buckling surgery, and patients with exudative RD were treated conservatively through observation in the clinic. Cases were presumed exudative if they developed RD with no history of retinal breaks after the completion of the systemic

chemotherapy whereas cases were presumed rhegmatogenous if they had developed RD after the completion of their chemotherapy and had previous retinal holes or tears treated with local retinopexy or cryotherapy. The patients with presumed exudative or rhegmatogenous RD features were treated conservatively.

## Surgical technique

Informed consent was obtained from all the parents of the patients. The procedure was performed under general anesthesia. A 360-degree conjunctival peritomy was performed followed by the slinging of all four rectus muscles. The location of the breaks was marked and cryotherapy applied. No external drainage was performed. A segmental silicone sponge was placed on the location of the breaks with a 5-0 polyester suture. An anterior chamber paracentesis was performed to ensure the optic nerve head was perfusing. No air or gas tamponade and posturing were required. Postoperative drops include a combination of mydrilate (cyclopentolate 0.5% or 1.0%) twice a day for two weeks and a mixed dexamethasone, neomycin sulphate, and polymyxin B sulphate drops four times a day for one month. Postoperative visits were on the first day, first week, and first month after the surgery. Further follow-up visits were dependable on the appearance of the RD and Rb.

## Results

A total of 258 children were treated for Rb over the 10-year period. 160 patients had unilateral Rb while 98 patients had bilateral Rb. Primary enucleation was performed in 139 patients with unilateral disease (86.88%) and one eye in 48 patients with bilateral disease (48.98%). A total of 169 eyes were managed with globe conserving treatment. Ten (5.92%) eyes of 10 patients were complicated with RD during treatment (Tables 1–3). The mean age of diagnosis of Rb was 6.4 months (range, 3–12 months). The mean age of diagnosis of RD was 12.3 months (range, 4–36 months). The Rb was bilateral in 8 out of 10 patients with RD. The ICRB classification was Group D in half of the patients with RD. In 8 patients, the RD occurred during systemic chemotherapy of which 6 had the RD occurring following the first chemotherapy cycle. The other 2 patients developed RD after their systemic chemotherapy had completed. Five patients were exudative or presumed exudative type of RD while the other 5 patients were rhegmatogenous or presumed rhegmatogenous RD.

## Exudative retinal detachment

Four of the 5 exudative RD eyes occurred after the first cycle of chemotherapy. Four patients did not have focal treatment prior to the development of RD, and RD resolved by conservative observational management. The other remaining RD patient was presumed to be exudative because it developed well over a year after completing systemic chemotherapy and within 3 weeks of IAC treatment with melphalan for multiple recurrences which had not responded to earlier plaque

Table 1  
Retinal detachment (RD) during retinoblastoma (Rb) management (Clinical characteristics).

Case No	Age at diagnosis of retinoblastoma months/sex	Rb laterality	ICRB	Systemic chemotherapy	Focal therapy	Status of fellow eye
1	6/F	BE	D	Yes	Yes	Regressed Rb
2	4/F	BE	C	Yes	Yes	Enucleated
3	3/M	BE	C	Yes	Yes	Regressed Rb
4	7/M	RE	C	Yes	Yes	No Rb
5	4/M	RE	D	Yes	No	No Rb
6	5/F	BE	D	Yes	Yes	Enucleated
7	6/M	BE	B	Yes	Yes	Regressed Rb
8	12/M	BE	B	Yes	Yes	Enucleated
9	9/M	BE	D	Yes	Yes	Regressed Rb
10	8/F	BE	D	Yes	No	Under treatment

Rb: Retinoblastoma; ICRB: International Classification of Retinoblastoma; F: Female; M: Male; BE: Both eyes; RE: Right eye.

Table 2  
Retinal detachment (RD) during retinoblastoma (Rb) management (Clinical characteristics).

Case No	Age at development of retinal detachment (Months)	RD during chemoreduction	Cycle of chemoreduction	Last local treatment before RD	Time interval since last local treatment	Retinal break or thinning
1	8	Yes	1st	None	N/A	No
2	5	Yes	1st	None	N/A	No
3	4	Yes	1st	None	N/A	No
4	5	Yes	1st	None	N/A	No
5	26	No	After	IAC	3 weeks	No
6	10	Yes	4th	Cryotherapy + subconjunctival Carboplatin	4 weeks	Yes
7	7	Yes	1st	Cryotherapy	4 weeks	Yes
8	13	Yes	5th	Laser	6 weeks	Yes
9	9	Yes	1st	None	N/A	Yes
10	36	No	After	Laser	6 weeks	No

RD: Retinal detachment; IAC: Intra-arterial chemotherapy with melphalan; N/A: Not applicable.

Table 3  
Retinal Detachment (RD) management and outcome.

Case No	RD type	Treatment	Time RD resolved	Final Rb status	Final vision
1	Exudative	Observation	20 weeks	Recurrence	No vision as had enucleation
2	Exudative	Observation	10 weeks	Regressed	0.2 Single Kays (20/32 Snellen)
3	Exudative	Observation	36 weeks	Regressed	0.86 Crowded Kays (20/145 Snellen)
4	Exudative	Observation	4 weeks	Under treatment	0.2 Single Kays (20/32 Snellen)
5	Presumed Exudative	Observation	Not resolved	Regressed	0.85 Crowded Kays (20/142 Snellen)
6	Rhegmatogenous	Scleral Buckle	6 weeks	Regressed	0.05 Crowded Kays (20/22 Snellen)
7	Rhegmatogenous	Scleral buckle	8 weeks	Regressed	0.2 Single Kays (20/32 Snellen)
8	Rhegmatogenous	Scleral buckle	4 weeks	Regressed	0.98 Crowded Kays (20/191 Snellen)
9	Rhegmatogenous	Scleral buckle	Not completely resolved	Regressed	1.84 Crowded Kays (20/1383 Snellen)
10	Presumed Rhegmatogenous	Observation	Not resolved	Regressed	HM

RD: Retinal detachment; Rb: Retinoblastoma; HM: Hand movements.

radiotherapy. Although the Rb had regressed with no recurrence, the RD did not resolve and had a complex picture of melphalan-induced chorioretinal atrophy around the RD. Two patients achieved VA of 0.2 Single Kays (20/32 Snellen), and the other two patients achieved 0.85 and 0.86 Crowded Kays (20/142 and 20/145 Snellen), respectively, after the RD had resolved. One patient developed tumor recurrence in their three year follow-up after resolution of RD, and the eye had to

be enucleated. The median time for the exudative RD to resolve is 15 weeks (range, 4–36 weeks).

#### *Rhegmatogenous retinal detachment*

Four of the 5 rhegmatogenous RD eyes occurred during the course of systemic chemotherapy. The cycle of chemotherapy after which the RD developed varied. The RD developed in the

first cycle in 2 cases, and fourth and fifth cycle in the other two patients, respectively (Table 2). Four patients developed rhegmatogenous RD within four to six weeks of focal therapy (cryotherapy or laser thermotherapy) (Fig. 1). External approach with scleral buckling procedure and cryotherapy was employed to repair the RD (Fig. 2). All cases were operated within 2 months of diagnosis of RD. In all operated cases, a retinal break or suspicious area of retinal thinning was identified before or during the operation. In 3 of the 4 operated patients, the median time for the retina to reattach was 6 weeks (range, 4–8 weeks). In the fourth patient, the retina did not reattach. The VA ranged between 0.05 Crowded Kays to 1.84 Crowded Kays (20/22 to 20/1384 Snellen). The fifth patient was presumed to be rhegmatogenous because the RD developed two years after systemic chemotherapy with concurrent multiple cryotherapy and thermotherapy sessions which suggests that there may be retinal thinning or atrophic holes that were not detectable clinically. Therefore, this patient was

managed conservatively. The Rb regressed in all the patients. None of the 5 patients with rhegmatogenous RD had to be enucleated for tumor recurrences. There were no intra- and postoperative complications noted.

## Discussion

Multi-agent systemic chemotherapy combined with local consolidation therapy is the preferred option in globe conserving treatment of Rb.<sup>1</sup> Complications like RD can occur during these treatments and cause practical difficulties in the management of Rb. Most of the published data about RD complicating Rb management occur following the use of EBRT along with systemic chemotherapy or other local cryoretinopexy or laser photocoagulation treatment.<sup>3–6</sup> There are a few case series of RD occurring during systemic chemotherapy with no EBRT.<sup>3,4,9,10</sup> We report ten patients (5.91%) which developed RD during primary chemoreduction which is similar to published studies which report a similar rate of around 6%.<sup>4,5</sup> In our study, 5 patients had features

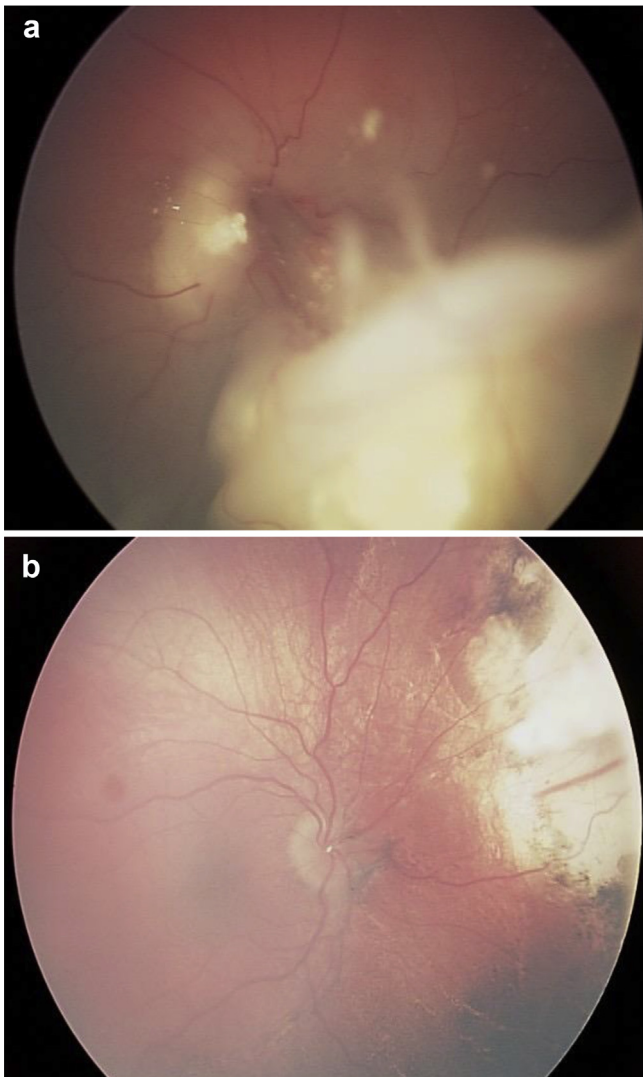


Fig. 1. a: Total retinal detachment (RD) within 4 weeks of cryotherapy and subconjunctival carboplatin. b: RD completely settled 6 weeks after scleral buckle surgery.

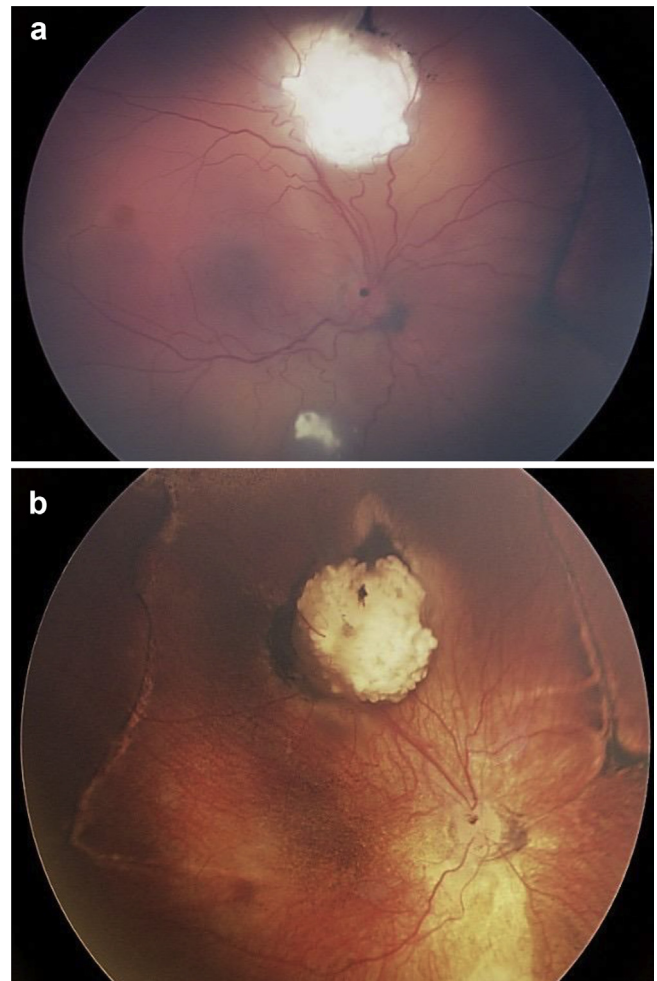


Fig. 2. a: Subtotal retinal detachment (RD) within 6 weeks of cryotherapy. b: Completely resolved RD 2 months after scleral buckle surgery.

suggestive of exudative RD while the other 5 patients had features suggestive of rhegmatogenous RD.

Exudative RD in Rb tends to present itself as an exophytic tumor when it grows subretinally, and this is associated with significant subretinal seeding of the tumor.<sup>1</sup> With systemic chemotherapy, exudative RD resolves as the Rb shrinks. However, in our case series, four of the 5 exudative RD occurred after the first cycle of systemic chemotherapy without any local focal consolidation treatment. The significance of this finding is not entirely clear, but an excessive initial inflammatory response from chemoreduction or rapid shrinkage of the tumor could be the cause of the exudative RD. Recent treatment of Rb involves the use of IAC which involves the cannulation of the ophthalmic artery to deliver melphalan to the eye.<sup>11</sup> IAC has been shown to resolve 43% of total RD and 100% of partial RD related Rb.<sup>12</sup> However, Shields et al. reports that 6% of rhegmatogenous RD can occur after IAC as well, but this is mostly in advanced eyes with extensive endophytic tumor appearance and atrophic retinal hole after rapid tumor regression.<sup>13</sup> In our case series, we had one similar patient that has developed a presumed exudative RD rather than a rhegmatogenous RD three weeks after the first cycle of IAC with melphalan. The RD did not resolve despite the regression of the Rb and showed a final complex picture of melphalan-induced chorioretinal atrophy combined with retinal pigment epithelial (RPE) changes around the RD. This similar complication was also described by Muen et al. where they had a case of a mixed tractional exudative RD developed after IAC with melphalan.<sup>14</sup>

It has been known that local cryotherapy and photocoagulation causes atrophy of the retina and choroid.<sup>15</sup> This can therefore induce inflammation and increase tractional forces at the vitreoretinal interface leading to the increase risk of developing small retinal holes that causes rhegmatogenous RD. Rhegmatogenous RD associated with Rb is commonly repaired with non-drainage or drainage scleral buckling. The success rate of retinal reattachment following scleral buckling is variable. In a 20-year retrospective study of Rb treated cases by Bauman et al., 5 of the 9 eyes with RD reattached after scleral buckling, but 3 eyes needed enucleation due to the recurrence of the Rb.<sup>3</sup> Other studies using similar techniques had a mixed final retina reattachment rate such as Tawansy et al.<sup>4</sup> (5 out of 14 cases), Bovey,<sup>5</sup> (2 out of 5 cases), Lim et al.<sup>6</sup> (3 out of 5 cases), Saumya et al.<sup>7</sup> (7 out of 7 cases), and Yousef et al.<sup>8</sup> (2 out of 3 cases). Most redetachment cases are due to the recurrence of the Rb which tends to lead to enucleation after the failed RD procedure.<sup>3</sup> Another surgical risk factor influencing the success rate of scleral buckling includes the tractional element of the condition.<sup>8</sup> Four of our 5 rhegmatogenous RD cases developed within four to six weeks after focal therapy of the Rb. These cases were treated with scleral buckling surgery, and 3 cases successfully reattached after 1–2 months. One of our cases was presumed to be rhegmatogenous due to the absence of a retinal break and the long evolution of the RD after systemic chemotherapy, which is not typical of an exudative RD. This

is similar to the findings by Bovey et al. and Anagnoste et al.<sup>5,9</sup> We did not conduct pars plana vitrectomy surgery in any of our patients, but Saumya et al. reported a successful reattachment of two of their cases with vitrectomy combined with tumor recession through retinectomy using melphalan infusion and silicone oil tamponade.<sup>7</sup> Combined vitrectomy with membrane peeling and scleral buckling with gas or silicone oil tamponade has also been reported to be successful in a small case series of three patients with RD with regressed Rb as it helps closed irregular shaped retinal tears at the edge of the tumor scars.<sup>16</sup>

This study has its limitations from the small number of patients and the retrospective nature of study. However, as Rb cases are rare, the findings from this study will help contribute to the pool of knowledge in the management of Rb related RD. In conclusion, exudative RD is a known complication during the systemic chemotherapy for Rb. With long-term conservative management through observation, exudative Rb will tend to resolve by itself. However, supplementary local focal treatment during the systemic treatment of Rb can lead to an increased risk of rhegmatogenous RD. In these situations, most rhegmatogenous RD can be successfully repaired with non-drainage scleral buckling and cryoretinopathy.

## References

- Shields JA, Shields CL. Management of retinoblastoma. In: Shields JA, Shields CL, eds. *Intraocular Tumors: An Atlas and Textbook*. Philadelphia, PA: Lippincott Williams Wilkins; 2008:334–351.
- Epstein JA, Shields CL, Shields JA. Trends in the management of retinoblastoma: evaluation of 1,196 consecutive eyes during 1974–2001. *J Pediatr Ophthalmol Strabismus*. 2003;40(4):196–203.
- Bauman CR, Shields CL, Shields JA, Tasman WS. Surgical repair of rhegmatogenous retinal detachment after treatment for retinoblastoma. *Ophthalmology*. 1998;105(11):2134–2139.
- Tawansy KA, Samuel MA, Shammas M, Murphree AL. Vitreoretinal complications of retinoblastoma treatment. *Retina*. 2006;26(7 Suppl):S47–S52.
- Bovey EH, Fernandez-Ragaz A, Héon E, Balmer A, Munier FL. Rhegmatogenous retinal detachment after treatment of retinoblastoma. *Ophthalmic Genet*. 1999;20(3):141–151.
- Lim TH, Robertson DM. Presumed rhegmatogenous retinal detachment in patients with retinoblastoma. *Retina*. 2000;20(1):22–27.
- Saumya Pal S, Gopal L, Khetan V, Nagpal A, Sharma T. Rhegmatogenous retinal detachment following treatment for retinoblastoma. *J Pediatr Ophthalmol Strabismus*. 2010;47(6):349–355.
- Yousef YA, Manna M, Khalil MB, Nawaiseh I. Surgical repair of rhegmatogenous retinal detachment in eyes harboring active retinoblastoma. *Ophthalmic Genet*. 2016;37(3):314–317.
- Anagnoste SR, Scott IU, Murray TG, Kramer D, Toledano S. Rhegmatogenous retinal detachment in retinoblastoma patients undergoing chemoreduction and cryotherapy. *Am J Ophthalmol*. 2000;129(6):817–819.
- Benz MS, Scott IU, Murray TG, Kramer D, Toledano S. Complications of systemic chemotherapy as treatment of retinoblastoma. *Arch Ophthalmol*. 2000;118(4):577–578.
- Abramson DH, Dunkel IJ, Brodie SE, Kim JW, Gobin YP. A Phase I/II study of direct intraarterial (ophthalmic artery) chemotherapy with melphalan for intraocular retinoblastoma initial results. *Ophthalmology*. 2008;115(8):1398–1404.
- Shields CL, Kaliki S, Shah SU, Bianciotto CG, Jabbour P, Shields JA. Effect of intraarterial chemotherapy on retinoblastoma-induced retinal detachment. *Retina*. 2012;32(4):799–804.

13. Shields CL, Say EAT, Pefkianaki M, et al. Rhegmatogenous retinal detachment after intraarterial chemotherapy for retinoblastoma: the 2016 founders award lecture. *Retina*. 2017;37(8):1441–1450.
14. Muen WJ, Kingston JE, Robertson F, Brew S, Sagoo MS, Reddy MA. Efficacy and complications of super-selective intra-ocular artery melphalan for the treatment of refractory retinoblastoma. *Ophthalmology*. 2012;119(3):611–616.
15. Lincoff H, Long R, Marquardt J, McLean J. The cryosurgical adhesion. *Trans Am Acad Ophthalmol Otolaryngol*. 1968;72(2):191–202.
16. Tanaka M, Yokoi T, Ito M, et al. Three cases of rhegmatogenous retinal detachment associated with regressed retinoblastoma after conservative tumor therapy. *Retin Cases Brief Rep*. 2014 Summer;8(3): 223–226.