Preservation of retinoblastoma group E eyes with neovascular glaucoma using intravenous chemotherapy: risk factors and outcomes

Article *in* British Journal of Ophthalmology · February 2019

DOI: 10.1136/bjophthalmol-2018-313442

CITATIONS
3

READS
130

3 authors, including:

Raksha Rao
Narayana Nethralaya
31 PUBLICATIONS **144** CITATIONS
SEE PROFILE

Santosh Honavar
Center for Sight
277 PUBLICATIONS **5,578** CITATIONS
SEE PROFILE

Preservation of retinoblastoma group E eyes with neovascular glaucoma using intravenous chemotherapy: risk factors and outcomes

Raksha Rao,[1] Santosh G Honavar,[2] Vijayanand Palkonda Reddy[1]

[1]Ocular Oncology Service, Centre for Sight, Hyderabad, India
[2]National Retinoblastoma Service, Ocular Oncology, Centre for Sight, Hyderabad, India

Correspondence to
Dr Santosh G Honavar, National Retinoblastoma Foundation, Ocular Oncology Service, Centre for Sight, Hyderabad 500034, India; santosh.honavar@gmail.com

Received 29 October 2018
Revised 24 January 2019
Accepted 29 January 2019

ABSTRACT

Background/aim To report the outcomes of retinoblastoma group E eyes with neovascular glaucoma (NVG) treated conservatively with intravenous chemotherapy and investigate factors associated with eye salvage and secondary enucleation.

Methods This is a retrospective, comparative, interventional case series. The outcome measures were life salvage, eye salvage and vision salvage.

Results Of the 37 eyes managed by intravenous chemotherapy, secondary enucleation was necessary in 21 eyes (group 1) and eye salvage was possible in 16 eyes (group 2). A comparison of both groups revealed significant difference with group 1 demonstrating greater duration of symptoms (18.8 weeks vs 5.4 weeks, p=0.016), greater intraocular pressure (IOP) at presentation (36 mm Hg vs 30 mm Hg, p=0.044), greater increase in corneal diameter (1.52 mm vs 0.50 mm, p=0.013) and the presence of sterile orbital cellulitis (9 vs 1, p=0.023). Further, the risk factors for secondary enucleation by univariate analysis were duration of symptoms >10 weeks (p=0.003), presenting IOP >26 mm Hg (p=0.045), buphthalmos (p=0.014) and sterile orbital cellulitis (p=0.023) and by multivariate analysis were age at presentation >6 months (p=0.012) and buphthalmos (p=0.017). At a mean follow-up of 20.5 months, none of the patients in either group developed systemic metastasis.

Conclusion For retinoblastoma group E eyes presenting with NVG, the chance of eye salvage with intravenous chemotherapy is better when the age at diagnosis is <6 months, duration of symptoms is <10 weeks, IOP is <26 mm Hg, and in the absence buphthalmos and sterile orbital inflammation.

INTRODUCTION

With the introduction of intra-arterial chemotherapy, there has been a paradigm shift in the management of retinoblastoma.[1] Intra-arterial chemotherapy achieves excellent eye salvage rates in both early and advanced retinoblastoma.[1] However, standard triple-drug (vincristine+carboplatin+etoposide) intravenous chemotherapy (IVC) continues to be the primary modality of treatment for retinoblastoma in many parts of the world.[2–4] IVC alone can achieve an impressive tumour control in less advanced cases, with an eye salvage of 100%, 93% and 90% in international classification of intraocular retinoblastoma (ICRB) groups A, B and C, respectively.[2] When used as the first line of treatment in conjunction with the focal consolidation therapies, IVC can achieve up to 47%–63% eye salvage in group D eyes.[2 3]

There are very few studies which have reported the efficacy of IVC in group E eyes with advanced retinoblastoma, as most often they undergo primary enucleation.[2 4 5] In one study that compared the management of group E eyes using IVC with and without radiation, the eye salvage rate at a mean follow-up of 63 months was reported to be 45% with the use of IVC alone, versus 83% with a combination of IVC and low-dose external radiotherapy.[4] However, this study did not include any group E eyes with neovascularisation of iris (NVI), neovascular glaucoma (NVG), extensive hyphema, extensive vitreous haemorrhage, tumour invasion into the anterior chamber, iris, optic nerve, choroid or eyes with massive tumour, total retinal detachment, extensive tumour seeding or sterile orbital cellulitis.[4] Long-term results indicate that secondary enucleation is necessary in many of the group E eyes for early and late treatment failure.[2 4 6] Despite this, IVC in group E eyes may still be indicated when there is bilateral group E disease, when it is the only eye of the patient or when the opposite eye requires IVC for less advanced retinoblastoma.[4 6]

The term neoadjuvant chemotherapy has been used in oncology to refer to chemotherapy given before any local therapy.[7] In advanced retinoblastoma, neoadjuvant intravenous chemotherapy is given with an intent to enucleate the eye, with a primary aim to control any immediate extraocular tumour extension and thus minimise the risk of systemic metastasis.[8] In addition, group E eyes with NVG may have thin sclera secondary to buphthalmos.[9 10] Neoadjuvant chemotherapy reduces the tumour load within the eye and helps make enucleation safer.[9 10] Here, we analyse the effect of intravenous chemotherapy in group E eyes with NVG and the clinical features contributing to failure of eye salvage in these eyes.

METHODS

Our retrospective, comparative, interventional case series included 59 eyes of 59 patients with ICRB group E retinoblastoma with NVG. The study setting was a tertiary care eye hospital with an integrated retinoblastoma management centre. Institutional review board approval was obtained.

The medical records of 59 patients with group E retinoblastoma with neovascular glaucoma were retrospectively reviewed. Demographic data included age at presentation (in months), gender

To cite: Rao R, Honavar SG, Reddy VP. *Br J Ophthalmol* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/bjophthalmol-2018-313442

(male, female), race (Asian Indians, others) and familial retinoblastoma (yes, no). Ocular features included laterality (unilateral, bilateral), affected eye (right, left), visual acuity at presentation, presenting symptom, duration of symptoms (in weeks), intraocular pressure (IOP, mm Hg) at presentation under sevoflurane anaesthesia immediately after induction, conjunctival congestion (present, absent), corneal oedema (present, absent), difference in the corneal diameter between both eyes (mm), anterior chamber depth (shallow or normal), anterior chamber seeds (present, absent), hyphema (present, absent), iris infiltration (present, absent), angle infiltration (present, absent), ectropion uveae (present, absent), peripheral synechiae (present, absent), NVI (focal, diffuse, absent), NVG (present, absent), cataract (present, absent), eyelid oedema (present, absent), proptosis (present, absent), sterile orbital cellulitis (present, absent), tumour occupying >75% of vitreous cavity (yes, no) and tumour thickness by ultrasound (mm). NVG was defined as the presence of NVI and IOP ≥22 mm Hg, with or without buphthalmos (difference between corneal diameter of both eyes ≥0.5 mm), with or without corneal oedema. Sterile orbital cellulitis was defined as preseptal or orbital inflammation associated with advanced intraocular retinoblastoma, clinically manifesting as eyelid oedema and erythema with or without proptosis, in the absence of clinical infection and radiological orbital tumour extension. All patients underwent MRI to rule out optic nerve extension, and scleral and extrascleral involvement. Baseline systemic work-up (paediatric oncology evaluation, cerebrospinal fluid analysis and bone marrow biopsy) was done to rule out metastasis.

Patients were managed by either primary enucleation or IVC with a combination of vincristine (0.05 mg/kg body weight on day 1), carboplatin (18.6 mg/kg body weight on day 1) and etoposide (5 mg/kg body weight on days 1 and 2) for a minimum of six cycles given every 4 weeks. Chemotherapy was extended to a maximum of 12 cycles if there was a hope for eye and vision salvage. For those with extensive vitreous seeds, periocular topotecan (2 mg/2 mL) was given concurrently with neoadjuvant chemotherapy, and intravitreal topotecan (30 µg/0.15 mL) was administered after the completion of systemic chemotherapy for any persistent or recurrent vitreous seeds every 3 weeks. Transpupillary thermotherapy or cryotherapy was used for small recurrent retinal tumours or subretinal seeds, and plaque radiotherapy for larger recurrent retinal tumours. Those with uncontrollable tumour or phthisis bulbi after the completion of neoadjuvant chemotherapy were managed by enucleation. The high-risk histopathological features (yes, no) and the need for adjuvant chemotherapy (yes, no) or radiotherapy were noted. The duration of follow-up (months), recurrence of the tumour (yes, no), systemic metastasis (yes, no) and the visual acuity of the salvaged eyes at the last follow-up were recorded. The clinical data were tabulated and analysed with regard to the main outcome measures—life salvage, eye salvage and vision salvage. All statistical calculations were performed using GraphPad software (GraphPad Software, San Diego, California, USA). The outcomes from each group were evaluated using the two-tailed Fisher exact test for categorical variables. For continuous variables, the Student t-test was employed. P values of 0.05 or lower were considered statistically significant. Logistic regression analysis was performed to assess the risk factors predictive of secondary enucleation.

RESULTS

Of the 59 eyes of 59 patients presenting with retinoblastoma with NVG, 22 eyes underwent primary enucleation and were excluded from the study. The reasons for primary enucleation included presence of hyphema or vitreous haemorrhage that precluded visualisation of the tumour, and suspicious choroidal and/or optic nerve invasion on imaging.

Table 1 Retinoblastoma with neovascular glaucoma: patient demographics

	Secondary enucleation (%), n=21	Eyes salvaged (%), n=16	P value	Total (%), n=37
Mean age (median, range), months	24.5 (21.1, 3.6–58.4)	18.0 (13.8, 2.4–51.8)	0.22	24.5 (21.1, 3.6–58.4)
Sex				
Male	11 (52)	9 (56)		20 (54)
Female	10 (48	7 (44)	1	17 (46)
Race				
Asian Indians	21 (100)	16 (100)		37 (100)
Others	0 (0)	0 (0)	1	0 (0)
Familial retinoblastoma				
Yes	0 (0)	0 (0)		0 (0)
No	21 (100)	16 (100)	1	37 (100)
Laterality				
Unilateral	14 (67)	10 (65)		24 (65)
Bilateral	7 (33)	6 (38)	1	13 (35)
Affected eye				
Right	8 (38)	7 (44)		15 (41)
Left	13 (62)	9 (56)	0.749	22 (59)

P value for categorical variables using Fisher exact test. P value for continuous variables using Student t-test.

There were 37 eyes of 37 patients that received neoadjuvant chemotherapy and were included for analysis, of which 21 eyes were secondarily enucleated (group 1) and 16 eyes were salvaged (group 2). The patient demographics are listed in table 1. The mean age at presentation of groups 1 and 2 was 24.5±16 and 18±15 months, respectively.

The tumour features are listed in table 2. The mean visual acuity in both groups was no fix and follow to light. A comparison of tumour features (group 1 vs group 2) demonstrated a significant difference between the two groups with regard to the mean duration of symptoms (18.8 weeks vs 5.4 weeks, p=0.016), mean presenting IOP (30 mm Hg vs 26 mm Hg, p=0.045) and mean difference in corneal diameter (1.5 mm vs 0.5 mm, p=0.014). There was also a significant difference with regard to the presence of lid oedema (9 vs 1, p=0.023) and sterile orbital cellulitis (9 vs 1, p=0.023) at presentation. No other tumour features showed any significant difference.

The treatment parameters are listed in table 3. There was no significant difference between the two groups with regard to the number of cycles of neoadjuvant chemotherapy. The group 1 eyes were secondarily enucleated for suboptimal response to neoadjuvant chemotherapy or tumour recurrence (13/21, 62%), phthisis (7/21, 33%) and vitreous haemorrhage (1/21, 5%). Of these, five (24%) had histopathological high-risk factors for which the patients further received adjuvant chemotherapy.

The treatment outcomes are listed in table 4. There was no statistical difference in the follow-up duration between the two groups (20.9 months vs 19.9 months, p=0852). In group 2 eyes, the main tumour recurrence was seen in 11 eyes (69%), subretinal seed recurrence in 5 eyes (31%) and vitreous seed recurrence in 5 eyes (31%), and all were successfully treated. There was no difference between groups 1 and 2 with regard to life

Table 2 Retinoblastoma with neovascular glaucoma: clinical features

	Secondary enucleation (%), n=21	Eyes salvaged (%), n=16	P value	Total (%), n=37
Visual acuity at presentation				
Fix and follow light	0 (0)	0 (0)	1	0 (0)
No fix and follow	20 (95)	15 (94)	1	35 (95)
Light perception	0 (0)	1 (6)	0.432	1 (3)
No light perception	1 (5)	0 (0)	1	1 (3)
Presenting symptom				
Leukocoria	18 (86)	15 (94)	0.618	33 (89)
Strabismus	2 (10)	0 (0)	0.496	2 (5)
Redness	0 (0)	1 (6)	0.432	1 (3)
Periocular swelling	1 (5)	0 (0)	1	1 (3)
Mean duration of symptoms (median, range), weeks	18.8 (12, 0.3–60)	5.4 (3, 1–28)	0.016	13 (8, 0.3–60)
Mean intraocular pressure* (median, range), mm Hg	30 (28, 22–42)	26 (25, 18–38)	0.045	28 (26, 18–42)
Conjunctival congestion				
Yes	21 (100)	15 (94)		36 (97)
No	0 (0)	1 (6)	0.432	1 (3)
Corneal oedema				
Yes	20 (95)	15 (94)		35 (95)
No	1 (5)	1 (6)	0.444	2 (5)
Mean difference in corneal diameter (median, range), mm	1.5 (1.0, 0–5)	0.5 (0, 0–2)	0.014	1.1 (0.5, 0–5)
Anterior chamber depth				
Shallow	4 (19)	6 (38)		10 (27)
Normal	17 (81)	10 (63)	0.274	27 (73)
Anterior chamber seeds				
Yes	3 (14)	0 (0)		3 (8)
No	18 (86)	16 (100)	0.243	34 (92)
Hyphema				
Yes	3 (14)	0 (0)		3 (8)
No	18 (86)	16 (100)	0.243	34 (92)
Iris infiltration				
Yes	0 (0)	0 (0)		0 (0)
No	21 (100)	16 (100)	1	37 (100)
Angle infiltration				
Yes	0 (0)	0 (0)		0 (0)
No	21 (100)	16 (100)	1	37 (100)
Ectropion uveae				
Yes	1 (5)	3 (19)		4 (11)
No	20 (95)	13 (81)	0.559	33 (89)
Peripheral synechiae				
Yes	2 (10)	1 (6)		3 (8)
No	19 (90)	15 (94)	1	34 (92)
Neovascularisation of iris				
Focal	1 (5)	1 (6)		2 (5)
Diffuse	20 (95)	15 (94)	1	35 (95)
Cataract				
Yes	0 (0)	0 (0)		0 (0)
No	21 (100)	16 (100)	1	37 (100)
Lid oedema				
Yes	9 (43)	1 (6)		10 (27)
No	12 (57)	15 (94)	0.023	27 (73)
Proptosis				
Yes	2 (10)	0 (0)		2 (5)
No	19 (90)	16 (100)	0.496	35 (95)
Sterile orbital cellulitis				
Yes	9 (43)	1 (6)		10 (27)
No	12 (57)	15 (94)	0.023	27 (73)
Tumour occupying >75% vitreous activity				

Continued

Table 2 Continued

	Secondary enucleation (%), n=21	Eyes salvaged (%), n=16	P value	Total (%), n=37
Yes	21 (100)	16 (100)		37 (100)
No	0 (0)	0 (0)	1	0 (0)
Mean tumour thickness (median, range), mm	19 (19, 18–20)	18 (18, 18–20)	0.884	19 (19, 18–20)

*Under sevoflurane anaesthesia. P value for categorical variables using Fisher exact test. P value for continuous variables using Student t-test.

salvage (100% vs 100%, p=1.000). Nine eyes (56%) of the 16 salvaged eyes had vision better than 20/200 (figures 1 and 2).

The clinical risk factors that are predictive of a more aggressive clinical course in retinoblastoma with neovascular glaucoma that would eventually require secondary enucleation were calculated using univariate and multivariate analysis, and the ones with a significant p value are listed in table 5. On univariate analysis, age at presentation >6 months (p=0.055) showed a borderline significance as a risk for enucleation, while the other factors with definite significance were duration of symptoms >10 weeks (p=0.003), presenting IOP >26 mm Hg (p=0.045), difference between the corneal diameters of both eyes ≥0.5 mm (p=0.015) and presence of sterile orbital cellulitis (p=0.023). On multivariate analysis, only age at presentation >6 months (p=0.012) and difference between the corneal diameters of both eyes ≥0.5 mm (p=0.017) were found to be statistically significant.

DISCUSSION

According to ICRB, group E eyes are defined as eyes with extensive retinoblastoma occupying >50% of the eye, media opacity secondary to vitreous haemorrhage or hyphema, presence of anterior segment invasion, presence of sterile orbital cellulitis, phthisis bulbi and presence of NVG.[2 11] The incidence of NVI with secondary glaucoma in retinoblastoma is approximately 12%.[5 9 12 13] NVG in retinoblastoma occurs secondary to peripheral anterior synechiae formation, which results from NVI due to retinal ischaemia caused by occlusion of the central retinal vessels by the large tumours.[13] NVG contributes to approximately 74% of secondary glaucoma in retinoblastoma.[14] Less frequently, glaucoma in retinoblastoma may also occur secondary to massive retinal detachment with subsequent pupillary block and clogging of the trabecular meshwork by the tumour cells.[5 13] Although medical management can be initiated for glaucoma in retinoblastoma, the presence of NVG generally indicates poor prognosis and subsequent need for enucleation.[9 15]

In oncology practice, neoadjuvant chemotherapy offers several advantages.[7 16 17] Apart from reducing the tumour volume and achieving tumour consolidation to facilitate focal therapies, it offers a possibility for organ salvage.[7 12 13 16 17] Systemic chemotherapy, with or without radiotherapy, when initiated before any local therapy, reduces the chances of local and systemic tumour spread and improves the overall patient survival.[7 17] A greater survival benefit was reported for patients with head and neck cancer who were administered neoadjuvant systemic chemotherapy.[16] The study further showed that organ preservation after neoadjuvant chemotherapy did not have any deterrent effect on patient survival.[16]

In ocular oncology, neoadjuvant systemic chemotherapy has been used successfully in primary and secondary orbital tumours in an attempt to avoid exenteration, thus allowing for local tumour resection and reducing morbidity to the patients.[17 18]

Table 3 Retinoblastoma with neovascular glaucoma: treatment

	Secondary enucleation (%) n=21	Eyes salvaged (%), n=16	P value	Total (%), n=37
Mean cycles of neoadjuvant chemotherapy (median, range)	6 (6, 6–12)	6 (6, 6–9)	0.298	6 (6, 6–12)
Adjuvant treatment				
TTT/cryotherapy	4 (19)	7 (44)	0.151	11 (30)
Periocular topotecan	1 (5)	1 (6)	1	2 (5)
Intravitreal topotecan	1 (5)	5 (31)	0.062	6 (16)
Plaque brachytherapy	2 (10)	1 (6)	1	3 (8)
Enucleation	21 (100)	0 (0)	<0.001	21 (57)
Suboptimal response to chemoreduction/tumour recurrence	13 (62)	0 (0)	<0.001	13 (35)
Phthisis	7 (33)	0 (0)	0.012	7 (19)
Vitreous haemorrhage	1 (5)	0 (0)	1	1 (3)
Histopathological risk factors				
Yes	5 (24)	0 (0)	–	5 (14)
No	16 (76)	0 (0)	–	14 (38)
Adjuvant chemotherapy				
Yes	5 (24)	0 (0)	–	5 (14)
No	16 (76)	0 (0)	–	14 (38)

P value for categorical variables using Fisher exact test. P value for continuous variables using Student t-test.
TTT, transpupillary thermotherapy.

Table 4 Retinoblastoma with neovascular glaucoma: outcomes

	Secondary enucleation (%), n=21	Eyes salvaged (%), n=16	P value	Total (%), n=37
Mean duration of follow-up (median, range), months	20.9 (21.5, 5.3–36.3)	19.9 (16.6, 4.0–85.7)	0.852	20.5 (19.5, 4.0–85.7)
Tumour recurrence				
Main tumour	5 (24)	11 (69)*	0.009	16 (43)
Subretinal seeds	0 (0)	5 (31)*	0.01	5 (14)
Vitreous seeds	1 (5)	5 (31)*	0.066	6 (16)
Life salvage				
Yes	21 (100)	16 (100)		37 (100)
No	0 (0)	0 (0)	1	0 (0)
Eye salvage				
Yes	0 (0)	16 (100)		16 (43)
No	21 (100)	0 (0)	<0.001	21 (57)
Final visual acuity				
20/20–20/200	–	9 (56)	–	9 (24)
20/200–FC	–	5 (31)	–	5 (14)
PL	–	2 (13)	–	2 (5)

P value for categorical variables using Fisher exact test. P value for continuous variables using Student t-test.
FC, Finger counting. PL, Perception of light.
*The total number exceeds the total number of eyes as some eyes had more than one type of recurrence.

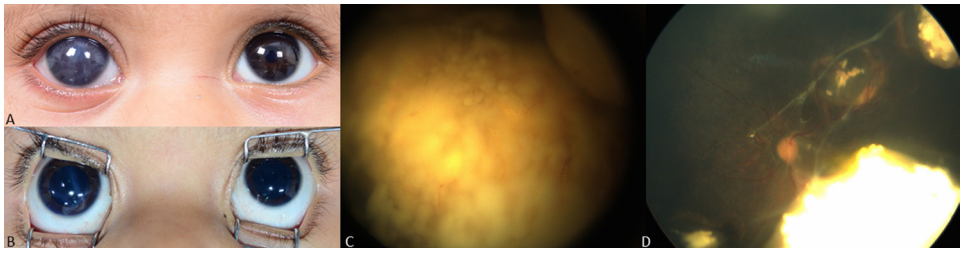

Figure 1 Retinoblastoma group E eye with neovascular glaucoma with eye salvage. (A) External photograph of a 3-month-old female shows right eye corneal oedema, buphthalmos, neovascularisation of iris (NVI) (not evident in the figure) and intraocular pressure (IOP) of 38 mm Hg. (C) Fundus imaging demonstrates a very large endophytic tumour filling the eye. The patient received neoadjuvant systemic chemotherapy×6 cycles with focal consolidation therapy, and at 11 months' follow-up, (B) the external photograph (under anaesthesia) reveals clear cornea, regressed NVI with an IOP of 12 mm Hg. (D) Fundus imaging shows regressed retinoblastoma with an intact fovea.

Systemic chemotherapy has also been shown to be beneficial even in advanced retinoblastoma.[8 9] In 2016, Shields *et al* described two patients where eye salvage and visual preservation were obtained in eyes with diffuse anterior retinoblastoma by systemic chemotherapy followed by plaque radiotherapy.[8] In a yet another case of diffuse anterior retinoblastoma, eye salvage was achieved solely with the use of systemic and local chemotherapy.[19]

Traditionally, eyes with advanced retinoblastoma presenting with NVG are enucleated.[2 5 9] In 2009, Parvus *et al* reported a single patient with bilateral retinoblastoma having buphthalmos from secondary glaucoma in one eye.[9] The patient received IVC for a total of six cycles with focal consolidating therapies, and at 18 months' follow-up, the buphthalmic eye remained stable with complete tumour regression and normal IOP.[9] In this series, systemic chemotherapy was initiated in the patients with an intent for safer enucleation and to optimise vision in the better eye in bilateral cases.[10 12] Chemotherapy helps by reducing the tumour volume and intraocular inflammation, and thus the risk of scleral perforation and subsequent orbital seeding during enucleation in a buphthalmic eye can be minimised.[9 10] However, in our series, eye salvage was possible in 16 of 37 eyes (43%) that received protocol-based systemic chemotherapy.

The study also recognises certain clinical features where eye salvage is possible in advanced retinoblastoma with NVG. In this series, eyes which were secondarily enucleated had one or more of the following risk factors which included age at presentation >6 months, greater duration of symptoms (>10 weeks), greater presenting IOP (≥26 mm Hg), presence of buphthalmos and presence of sterile orbital cellulitis. In a study of 105 eyes managed by systemic chemotherapy, Gündüz *et al* reported that older age at presentation is a risk factor predictive of enucleation.[20] The authors speculated that older age essentially implies late diagnosis and hence larger tumours at presentation.[21] In the current series, 19 of the 21 patients (90%) that underwent secondary enucleation were >6 months of age, suggesting that late diagnosis leads to larger tumours at presentation which tend to respond suboptimally to chemotherapy. Increased corneal diameter has been described as a risk factor for early treatment failure with IVC by Fabian *et al* in their study on group D eyes.[3] Greater age at presentation, greater duration of symptoms, higher IOP and presence of buphthalmos are likely to be indicative of larger and aggressive tumours, thus leading to failure of treatment with IVC. Additionally, 10 patients (n=10/37, 27%) in our series had sterile orbital cellulitis at presentation. Sterile orbital cellulitis in retinoblastoma occurs due to tumour necrosis and the associated necrotic changes in the iris and ciliary body, subsequently resulting in orbital inflammation.[21] With chemotherapy, nine eyes with severe orbital inflammation turned phthisical which were enucleated safely, while one eye with milder inflammation could be salvaged with chemotherapy and concomitant systemic steroids.

Certain studies have established that the presence of NVI, secondary glaucoma and buphthalmos indicate the presence of histopathological high-risk factors.[22–26] In a study of 84 eyes, Shields *et al* demonstrated that the presence of optic nerve invasion carried a greater metastatic risk, and higher IOP (>22 mm Hg) at presentation was a clinical feature predictive of optic nerve invasion (p=0.02).[22] In a similar study that assessed the risk for choroidal invasion, raised IOP (p=0.04) and the presence of NVI (p=0.007) were found to be important predictive factors.[23] Gupta *et al* reported that iris neovascularisation correlated well with the presence of both choroidal and retrolaminar optic nerve invasion.[26] The presence of buphthalmos and secondary glaucoma have also been established as clinical factors predictive of high-risk features on pathology.[25 26] In our study, none of the patients had choroidal and optic nerve invasion on imaging.

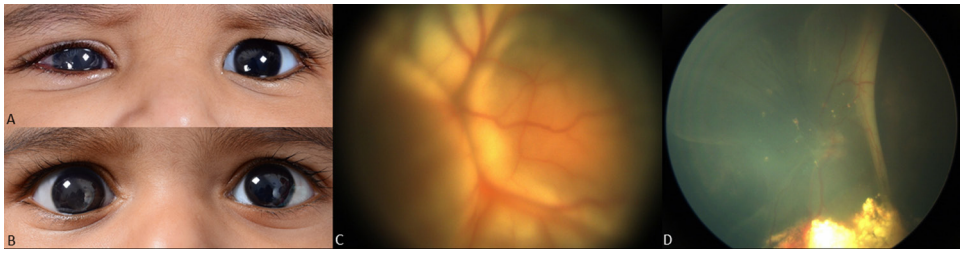

Figure 2 Retinoblastoma group E eye with neovascular glaucoma with eye salvage. (A) External photograph of a 4-month-old male reveals right eye (OD) corneal oedema, buphthalmos, neovascularisation of iris (NVI) (not evident in the figure) and intraocular pressure (IOP) of 32 mm Hg. (C) Fundus imaging demonstrates a very large exophytic tumour filling the eye. The patient received neoadjuvant systemic chemotherapy×6 cycles with focal consolidation therapy, and at 9 months' follow-up, (B) the external photograph reveals clear cornea, regressed NVI with an IOP of 8 mm Hg. (D) Fundus imaging shows regressed calcified retinoblastoma with a prominent retinal fold.

Table 5 Retinoblastoma with neovascular glaucoma: clinical risk factors predictive of secondary enucleation after neoadjuvant chemotherapy

			Univariate analysis		Multivariate analysis	
Feature	**Secondary enucleation (%), n=21**	**Eyes salvaged (%), n=16**	**OR (95% CI)**	**P value**	**OR (95% CI)**	**P value**
Age at diagnosis >6 months	19 (90)	6 (34)	5.7 (1 to 33.6)	0.055	77.36 (2.6 to 2296)	0.012
Duration of symptoms >10 weeks*	13 (62)	2 (13)	11.4 (2 to 63.8)	0.003	–	–
Presenting IOP >26 mm Hg	13 (62)	4 (25)	4.9 (1.2 to 20.5)	0.045	9.57 (0.74 to 124.1)	0.084
Difference in corneal diameter ≥0.5 mm	17 (81)	6 (38)	7.1 (1.6 to 31.3)	0.015	21.6 (1.72 to 271.4)	0.017
Presence of sterile orbital cellulitis	9 (43)	1 (6)	11.3 (1.2 to 101.6)	0.023	8.806 (0.62 to 125.1)	0.108

Binary logistic regression for the univariate and multivariate analysis.
*Due to co-linearity with age at diagnosis, the duration of symptoms was excluded in multivariable analysis.
IOP, intraocular pressure.

In the secondary enucleation group, five eyes (24%) which had histopathological high-risk factors were treated with adjuvant chemotherapy, and at final follow-up, none of the patients in either of the groups had an evidence of metastasis. Hence, the authors believe that if an attempt at eye salvage is considered in group E eyes with NVG with possible histopathological high-risk factors, IVC would be beneficial in patients with micrometastasis, helping in minimising the risk of systemic metastasis.

The retrospective nature of the study, small cohort size, relatively short follow-up and lack of sensitivity of MRI to detect early optic nerve invasion are the limitations of the study.[27 28] Nevertheless, the present study implies that eye salvage in retinoblastoma presenting with NVG is possible. Identifying the factors that are high risk for secondary enucleation can help categorise the patients to avoid systemic chemotherapy and also shorten the overall treatment time. However, systemic chemotherapy in advanced retinoblastoma as an eye salvage therapy must be undertaken with watchful monitoring, and only after ruling out the presence of gross extraocular and optic nerve extension.

Acknowledgements From the National Retinoblastoma Foundation, Ocular Oncology Service, Centre for Sight, Road No 2, Banjara Hills, Hyderabad 500034, India

Contributors All four authors made contributions to conception or design of the work, drafting of the work, revising it critically, approving the final version to be published, and are accountable for all aspects of the work, and ensure the accuracy or integrity of the work.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement SGH had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. No conflicting relationship exists for any author.

REFERENCES

1 Shields CL, Jorge R, Say EAT, *et al*. Unilateral retinoblastoma managed with intravenous chemotherapy versus intra-arterial chemotherapy. outcomes based on the International Classification of Retinoblastoma. *Asia Pac J Ophthalmol* 2016;5:97–103.
2 Shields CL, Mashayekhi A, Au AK, *et al*. The International Classification of Retinoblastoma predicts chemoreduction success. *Ophthalmology* 2006;113:2276–80.
3 Fabian ID, Stacey AW, Johnson KP, *et al*. Primary intravenous chemotherapy for group D retinoblastoma: a 13-year retrospective analysis. *Br J Ophthalmol* 2017;101:82–8.
4 Shields CL, Ramasubramanian A, Thangappan A, *et al*. Chemoreduction for group E retinoblastoma: comparison of chemoreduction alone versus chemoreduction plus low-dose external radiotherapy in 76 eyes. *Ophthalmology* 2009;116:544–51.
5 de Leon JMS, Walton DS, Latina MA, *et al*. Glaucoma in retinoblastoma. *Semin Ophthalmol* 2005;20:217–22.
6 Berry JL, Kogachi K, Aziz HA, *et al*. Risk of metastasis and orbital recurrence in advanced retinoblastoma eyes treated with systemic chemoreduction versus primary enucleation. *Pediatr Blood Cancer* 2017;64.
7 Trimble EL, Ungerleider RS, Abrams JA, *et al*. Neoadjuvant therapy in cancer treatment. *Cancer* 1993;72:3515–24.
8 Shields CL, Lally SE, Manjandavida FP, *et al*. Diffuse anterior retinoblastoma with globe salvage and visual preservation in 3 consecutive cases. *Ophthalmology* 2016;123:378–84.
9 Parvus BJ, Salazar PF, Shields CL, *et al*. Globe salvage using chemoreduction for advanced retinoblastoma in a glaucomatous eye with buphthalmos. *Retin Cases Brief Rep* 2009;3:1–3.
10 Shields CL*et al*. Factors predictive of recurrence of retinal tumors, vitreous seeds, and subretinal seeds following chemoreduction for retinoblastoma. *Arch Ophthalmol* 2002;120:460–4.
11 Murphree AL. Intraocular retinoblastoma: the case for a new group classification. *Ophthalmol Clin North Am* 2005;18:41–53.
12 Patel J, Turaka K, Shields CL. Resolution of iris neovascularization following chemoreduction of retinoblastoma. *J Pediatr Ophthalmol Strabismus* 2010;47.
13 Yoshizumi MO, Thomas JV, Smith TR. Glaucoma-inducing mechanisms in eyes with retinoblastoma. *Arch Ophthalmol* 1978;96:105–10.
14 Shields CL, Shields JA, Shields MB, *et al*. Prevalence and mechanisms of secondary intraocular pressure elevation in eyes with intraocular tumors. *Ophthalmology* 1987;94:839–46.
15 Walton DS, Grant WM. Retinoblastoma and iris neovascularization. *Am J Ophthalmol* 1968;65:598–9.
16 Urba SG, Wolf GT, Bradford CR, *et al*. Neoadjuvant therapy for organ preservation in head and neck cancer. *Laryngoscope* 2000;110:2074–80.
17 Murthy R, Honavar SG, Burman S, *et al*. Neoadjuvant chemotherapy in the management of sebaceous gland carcinoma of the eyelid with regional lymph node metastasis. *Ophthalmic Plast Reconstr Surg* 2005;21:307–9.
18 Savar A, Trent J, Al-Zubidi N, *et al*. Efficacy of adjuvant and neoadjuvant therapies for adult orbital sarcomas. *Ophthalmic Plast Reconstr Surg* 2010;26:185–9.
19 Rao R, Honavar SG, Mulay K, *et al*. Eye salvage in diffuse anterior retinoblastoma using systemic chemotherapy with periocular and intravitreal topotecan. *J Aapos* 2018;22:235–7.
20 Gündüz K, Günalp I, Yalçındağ N, *et al*. Causes of chemoreduction failure in retinoblastoma and analysis of associated factors leading to eventual treatment with external beam radiotherapy and enucleation. *Ophthalmology* 2004;111:1917–24.
21 Nalci H, Gündüz K, Erden E. Necrotic intraocular retinoblastoma associated with orbital cellulitis. *Surv Ophthalmol* 2017;S0039-6257:30154–0.
22 Shields CL, Shields JA, Baez K, *et al*. Optic nerve invasion of retinoblastoma. Metastatic potential and clinical risk factors. *Cancer* 1994;73:692–8.
23 Shields CL, Shields JA, Baez KA, *et al*. Choroidal invasion of retinoblastoma: metastatic potential and clinical risk factors. *Br J Ophthalmol* 1993;77:544–8.
24 Kaliki S, Srinivasan V, Gupta A, *et al*. Clinical features predictive of high-risk retinoblastoma in 403 Asian Indian patients: a case-control study. *Ophthalmology* 2015;122:1165–72.
25 Gupta R, Vemuganti GK, Reddy VA, *et al*. Histopathologic risk factors in retinoblastoma in India. *Arch Pathol Lab Med* 2009;133:1210–4.
26 Chantada GL, Gonzalez A, Fandino A, *et al*. Some clinical findings at presentation can predict high-risk pathology features in unilateral retinoblastoma. *J Pediatr Hematol Oncol* 2009;31:325–9.
27 Brisse HJ, de Graaf P, Galluzzi P, *et al*. Assessment of early-stage optic nerve invasion in retinoblastoma using high-resolution 1.5 Tesla MRI with surface coils: a multicentre, prospective accuracy study with histopathological correlation. *Eur Radiol* 2015;25:1443–52.
28 de Jong MC, de Graaf P, Brisse HJ, *et al*. European Retinoblastoma Imaging Collaboration (ERIC). The potential of 3T high-resolution magnetic resonance imaging for diagnosis, staging, and follow-up of retinoblastoma. *Surv Ophthalmol* 2015;60:346–55.