Long-term Visual Acuity, Strabismus and Nystagmus Outcomes Following Multimodality Treatment in Group D Retinoblastoma Eyes

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Short title: Long-term orthoptic outcomes in Group D retinoblastoma.

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ABSTRACT

Purpose

To analyse the long-term visual acuity, strabismus and nystagmus outcomes in Group D retinoblastoma following multimodality treatments in a national retinoblastoma referral centre.

Design

Retrospective interventional case series.

Methods

A 13-year retrospective chart review of Group D eyes treated initially with intravenous chemotherapy (IVC) and followed-up for at least 1 year from last treatment. Risk factors for final visual acuity (VA) were analysed, and rate of strabismus and nystagmus at last follow-up visit were calculated.

Results

One hundred and four Group D eyes (92 patients) presented to our centre during the study period, of which 32 (27 patients) met the inclusion criteria. Following IVC (vincristine, etoposide and carboplatin), adjuvant treatments included intra-ophthalmic artery chemotherapy in 5 (16%) eyes, plaque brachytherapy in 5 (16%), transpupillary thermotherapy (TTT) in 18 (56%) and cryotherapy in 24 (75%) eyes. On last examination, 64.41 ± 6.76 months from presentation, mean final VA was 20/283 (logMAR equivalent of 1.15±0.15). On univariate analysis, presentation age, foveal retinoblastoma (at initial examination), use of TTT and tumour-foveola distance (at last visit) were found to be significant risk factors for worse VA ($p<0.026$). On multivariate analysis, however, only TTT was found to be significant ($p=0.010$). At last visit, 6/27 (22%) patients had nystagmus and 12/20 (60%) of bilaterally salvaged patients had strabismus (n=10 exotropia and n=2 esotropia).

Conclusions

Following multimodality treatments initiated with IVC, 50% of salvaged Group D retinoblastoma eyes had <20/200 vision, with TTT being a risk factor for worse vision, 60% had strabismus and 22% nystagmus.

INTRODUCTION

Retinoblastoma management has undergone dramatic changes in the last 50 years, resulting in high survival rates, estimated at 98% in developed countries,[1] and high globe salvage rates, stratified according to grade of tumour burden.[2] Intravenous chemotherapy (IVC), first introduced in the 1990's,[3–6] was found to achieve >90% tumour control when used for International Intraocular Retinoblastoma Classification (IIRC)[7] groups A-C, and 47% in cases of group D eyes.[2] We have recently reported on 63% group D eye salvage rate using primary IVC, followed by adjuvant modalities as required.[8] Abramson et al. reported higher tumour control rates using primary intra-ophthalmic artery chemotherapy (IAC) for group D eyes.[9] Altogether, most D eyes today are successfully managed by conservative measures. Following globe salvage, the main concern focuses on functional outcomes, especially visual acuity.[10–15] There is only scant literature, however, on long-term visual outcomes of salvaged IIRC group D eyes,[10,14,16] and only a single report that focused purely on D eyes.[10]

Visually deprived children, as is the case with many retinoblastoma patients with a foveal tumour or detached fovea, are at risk of developing strabismus and/or nystagmus. Both conditions may result with negative psychosocial implications on the subjects' life.[17,18] At presentation, leucocoria is a more common feature than strabismus and far more common than nystagmus.[19] However, strabismus and nystagmus, may persist, worsen or develop at a later stage in retinoblastoma patients, features that are not covered in the retinoblastoma literature.

The goals of the present study were to report on the long-term visual and orthoptic outcomes in salvaged group D eyes following multimodality treatments, initiated by IVC. The specific aims were to evaluate the long-term visual outcomes in this population, to identify risk factors predictive of worse visual acuity (VA), and to report on the rate of nystagmus and strabismus present at last visit in this population.

METHODS

This was a retrospective chart review of consecutive IIRC group D cases[7] that presented to the London Retinoblastoma Service from 2002-2014 and were managed initially with IVC. Only salvaged eyes followed-up for 12 months or more from last treatment were included for analysis. The study was approved by the Barts Health NHS Trust institutional review board (number 6622), which waived the need to obtain informed consent from patients, and was executed in adherence to the Declaration of Helsinki.

Data retrieved from clinical notes included patients' age, gender, family history of retinoblastoma, clinical variables at presentation and throughout follow-up, genetic analysis results, treatment modalities, and orthoptic evaluation. All RetCam (Clarity Medical Systems, Pleasanton, CA, USA) images, as well as fluorescein angiograms for selected patients, at presentation and throughout follow-up, were reviewed and analysed. Fundus images at last follow-up visit (RetCam or fundus camera) were analysed with respect to distance (mm) of the nearest retinal tumour to the optic disc and foveola, choroidal ischaemia at the macula/extra-macular region, retinal pigment (RP) changes at the macula/extra-macular region, retinopathy (i.e. papillopathy, maculopathy and/or elsewhere at the retina), presence of retinal detachment at the macula/extra-macular region and tumour regression type.[20,21] Macular complications were recorded only in cases of tumours ≥1mm from the foveola.

IVC (vincristine, etoposide and carboplatin) was given via a central line, approximately once every 3 weeks, for 6 cycles. Focal treatments, given for tumour relapse, included cryotherapy, transpupillary thermotherapy (TTT) and ruthenium plaque brachytherapy. For cryotherapy, a cryosurgical system (Mira, Waltham, MA, USA) was used, and each treatment session included 3x freeze-thaw cycles, and for TTT (Iris Medical OcuLight SLx, Iridex Corporation, Mountain View, CA, USA), an 810nm indirect large laser spot beam was used. In cases of subfoveolar tumours, care was taken to spare the fovea during adjuvant treatment with TTT. IAC as adjuvant/salvage treatment was performed as described previously,[22] using melphalan and/or topotecan. Intra-vitreous chemotherapy (IViC) was first used in our service in 2014, hence none of the patients in the present cohort received this treatment.

Orthoptic evaluation at last visit included cover testing at near (1/3 m) and distance (6 m), ocular motility examination, nystagmus assessment and VA examination. Visual acuity was assessed using Cardiff acuity cards, Kays picture tests, Sheridan Gardiner Single letters, Sheridan Gardiner Linear letters, or Snellen acuity, depending upon the age of the child. Patients in whom a 2 line difference was found between eyes, after correction of refractive errors, were instructed for 2-4 hours/day patching treatment for amblyopia.

Statistical analysis

All calculations were performed using Microsoft Excel 2013 software (Microsoft Corporation, Redmond, WA, USA) and SPSS software version 17.0 (SPSS, Inc., Chicago, IL, USA). Snellen VA was converted to logMAR equivalent. Approximations for VA worse than 20/400 were as follows: counting fingers, 20/2000; hand motions, 20/4000; light perception, 20/8000; and no light perception, 20/16000.[23] Clinical correlations to final VA (a continuous variable) and to final VA worse than 20/200 (a categorical variable) were analyzed using Chi-square or Fisher's Exact Test for categorical variables and T-Test for continuous ones. Variables found significant ($P \leq 0.05$) on univariate analysis were further evaluated using multivariate analysis (Stepwise Linear Regression). Results throughout the manuscript are presented as mean ± standard error of the mean.

RESULTS

During the study period, 104 group D eyes of 92 patients presented and were treated in the London Retinoblastoma service. Of these, 40 eyes (of 40 patients) underwent primary enucleation and the remaining 64 (52 patients) eyes were treated initially with IVC. Of the 64 eyes, 24 had secondary enucleation and 40 were salvaged. Of the 40 eyes, 32 (27 patients) were followed-up for more than 12 months from last treatment and these comprise the study group (**Figure 1**). In terms of the 8th edition AJCC/UICC clinical staging system,[24] included were 1 (3%) eye classified as cT2aN0M0H0, 5 (16%) as cT2aN0M0H1, 6 (19%) as cT2bN0M0H0 and 20 (63%) as cT2bN0M0H1.

Table 1 summarizes the main demographic and clinical features of the study group. Of the 27 study patients, 9/27 (33%) presented with unilateral retinoblastoma, and the remaining 18/27 (67%) with bilateral disease. Of the bilateral cases, 9/18 (50%) were bilateral IIRC group D retinoblastoma (in 3 of these cases one D eye was enucleated and in one case, followed-up for less than 12 moths, hence these 4 eyes were not included for analysis), and the remaining were IIRC groups A (n=2), B (n=1), C (n=3) and E (n=3). Modes of presentation included leucocoria in 15/27 (56%), strabismus in 8/27 (30%), both leucocoria and strabismus in 3/27 (11%), and in a single (4%) patient the presenting sign was nystagmus. The age of presentation was 12.41 ± 9.90 months. There were 25/32 (78%) cases that had *RB1* mutation and 7/32 (22%) which also had a family history of retinoblastoma. Findings at first clinical examinations included retinoblastoma occupying the fovea in 23/32 (72%) cases, subretinal seeds in 17/32 (53%), vitreous seeds in 14/32 (44%) and a detached retina in 26/32 (81%) cases. Adjuvant treatments given after IVC included IAC in 5/32 (16%) cases (mean number of treatments: 3±1), plaque brachytherapy in 5/32 (16%) cases, TTT in 18/32 (56%) cases (mean number of applications: 2±0.5) and cryotherapy in 24/32 (75%) cases (mean number of applications: 3±0.8). External beam radiation (EBRT) was not used in any of the patients.

At last visit, tumour regression types were type I in 17/32 (53%) cases, type III in 14/32 (44%) and type IV in a single (3%) case, and tumour distances from the foveola and optic disc were 1.94 ± 0.52mm and 2.00 ± 0.44mm, respectively. Altogether, in 12/32 (37%) cases, tumours were located ≥1mm from the foveola. Choroidal ischaemia was present at the macula in 1/12 (8%) case and in the extra-macular region in 5/32 (16%) cases, 4 of which had previous IAC. Macular retinal pigment epithelial changes were present in 8/12 (67%) cases and extra-macular RP changes in 28/32 (88%) cases. Extra-macular radiation retinopathy was present in 5/32 (16%) cases, all of which previously had plaque brachytherapy. A detached macula was present in 1/12 (8%) case, a partially detached retina in 3/32 (9%) cases and a total retinal detachment in 1/32 (3%). Of the 12 cases in which the tumour was ≥1mm of the foveola, 9/12 (75%) showed one of these of macular abnormalities.

The mean final VA was 20/283 (logMAR vision equivalent of 1.15±0.15) but 7 (22%) cases had VA of 20/40 or better, and 16 (50%), VA of 20/200 or better. The total mean follow-up time was 64.41 ± 6.76 months and the interval from last treatment to last visit was 50.70 ± 7.08 months. On univariate analysis, variables at presentation that correlated with decreased final VA included young age of presentation (P=0.017) and foveal retinoblastoma (P=0.002). Additional significant variables were TTT (P=0.026) and distance of tumour to foveola at last visit (P=0.003). **Table 1** shows the univariate and **Table 2** the multivariate analysis results of the clinical correlations to decreased final VA. On multivariate analysis, the only significant variable found was TTT (P=0.010). Similar clinical variables were found to correlate on univariate analysis to final VA of 20/200 or worse, while TTT was the only predictor found on multivariate analysis (P=0.029).

Orthoptic evaluations to examine strabismus and nystagmus at the end of the study period are shown in **Table 3**. At last follow-up visit, 7/27 (26%) patients had one eye removed (1 group C, 3 group D and 3 group E). Of the 20/27 (74%) remaining patients, a form of strabismus (i.e. true, alternate or intermittent squint) was present in 15/20 (75%) of patients. Of these, true exotropia was the predominant form, present in 10/15 (67%) patients, and true esotropia in 2/15 (13%) patients. There were 2/20 (10%) patients that had in addition to the horizontal squint also a vertical component. None of the patients reported diplopia. Of note, at study closure, none of the patients had received strabismus surgery or botulinum toxin injections and none had developed cataract.

At last visit, 6/27 (22%) patients had nystagmus. Their mean age of presentation with retinoblastoma was 7.6±2.4 months. In all cases, patients had bilateral advanced (≥IIRC Group D or cT2N0M0) retinoblastoma, involving the fovea. Three patients (50%) had one eye enucleated (D eye remained) and in 3/6 (50%) had bilateral salvaged group D eyes. None of the patients had a pinealblastoma or other brain tumour. During the study period, none of the patients developed metastasis and all were alive.

DISCUSSION

Until recently, attempts to salvage IIRC group D eyes resulted with less than 50% success rate.[2] With the recent advent of IAC and IViC, salvage rates have increased considerably to reach >60% with first-line IVC and subsequent IAC as salvage,[8] and >80% when IAC was used as the primary treatment modality.[9] Initial attention is focused on controlling the disease, but once the child survives the cancer, there is usually some degree of ocular morbidity, that may affect quality of life. In the chemotherapy era, survivors of retinoblastoma (and their parents) are often concerned about visual acuity and residual squint. In this study we have attempted to evaluate our results from visual and orthoptic testing exclusively in Group D eyes at a mean follow-up of over 5 years, so that retinoblastoma specialists can more accurately counsel families. Our results have shown that nearly 50% of Group D eyes had VA of <20/200 and 75% had some form of strabismus.

There is little reported on visual outcomes of salvaged group D eyes following chemotherapy.[10,14,16] Batra et al. evaluated vision in 45 eyes classified as IIRC A-D, subgrouping them to A+B and C+D (n=27 eyes).[14] More than half of eyes in the latter subgroup had final VA of 20/40 or worse. No sub-analysis, however, was performed on D eyes. In that report, IIRC groups C+D patients were found to be at a higher risk of poor vision. Narang et al. determined the predictors of long-term visual outcomes after chemoreduction, including all IIRC groups, even Group E eyes.[16] In their cohort there were 22 group D eyes, 91% of which reached a final VA worse than 20/40. IIRC group was found to be a significant predictor for poor vision, among other factors, but on multivariate analysis only tumour distance to the fovea and number of tumours were found to play a role. There was no group D sub-analysis in that study. Berry et al. evaluated the outcomes of group D eyes of bilateral retinoblastoma patients treated with primary chemoreduction and EBRT (In the form of low-dose intensity modulated radiation therapy) as salvage.[10] Altogether, 45 eyes were salvaged, 24 of which were also treated with EBRT. However, logMAR vision was available only for 25 eyes; in 20 eyes visual acuity assessment was of fix and follow only, due to patients' age. In addition, some of the patients were followed-up for a relatively short period of less than one year. Of note, all of these studies were before the widespread introduction of IAC.

According to the present study salvaged group D eyes are equally likely to have vision worse than 20/200 (ambulatory vision). Younger patients, those with foveal tumours (as estimated on first examination or measured on last examination) and especially those treated with TTT were found to be at higher risk to have worse final vision. The main goal in treating retinoblastoma is to reach tumour control, to avoid metastatic spread and to save the globe, even at the risk of scarifying vision. TTT is a very efficient modality for posterior pole retinoblastoma, used as adjuvant to first-line chemotherapy as well as for tumour relapse, as is the indication in our service. As adjunct therapy, there is no consensus regarding the recommended timing of use – in every case in conjunction with chemotherapy, or as

required according to the response to chemotherapy.[5,25,26] Either way, as a focal treatment it is commonly used in eyes treated with systemic chemotherapy,[27] as well as in eyes treated with IAC.[9] Interestingly, Schefler at al. investigated the impact of systemic chemotherapy and TTT on macular retinoblastoma (Reese-Ellsworth groups I-V) in respect to visual functions and found that 11/14 (79%) had VA≥20/200 at final visit.[28] These excellent results, however, were not repeated in the present study.

Visual deprivation may result in strabismus, nystagmus and amblyopia, and in this cohort in 63% of eyes tumours were located <1mm from the fovea, and of the remaining eyes, 75% had macular abnormality associated with an adjacent tumour, detached retina and/or treatment side effects. Infantile nystagmus may further limit visual acuity due to the ocular oscillations and inability to maintain stable foveal fixation.[29] it was reported to develop in association with several ocular abnormalities, including foveal hypoplasia, optic nerve hypoplasia/dysplasia, optic atrophy, retinopathies and congenital cataract,[30] but to the best of our knowledge was not previously reported in association with retinoblastoma. Strabismus in this population could theoretically also be a result of extraocular muscle palsy after IAC.[31] However, this complication was not noted in the 5 study patients who received this treatment. Strabismus and nystagmus are known to be associated with psychosocial difficulties and have an overall adverse impact on patients' quality of life.[17,18,32] Strabismus was also found to adversely influence observers.[33] Interestingly, none of the children in the present cohort had squint surgery, some of whom were in their teenage years. Secondary sensory strabismus cases may benefit from eye muscle surgery, although this was not evaluated in retinoblastoma patients.[34] Having had multiple treatments for globe salvage under general anaesthesia in young age, it is possible that patients and families find surgical strabismus correction unappealing in later life.

The main limitation of this study is its retrospective design. For visual outcome analysis all clinical variables were available, and we could calculate risk factors for poor final vision. However, for strabismus and nystagmus, it was the final rates that were assessed. The presence of squint was always noted in the medical history, but an accurate orthoptic measurement at presentation was not always possible. Despite these constraints, this study is currently the largest to report on group D eyes' visual outcomes after multimodality treatments. To the best of our knowledge, it is also the first study to report on the rate of strabismus and nystagmus at last visit. As treatments evolve with wider use of IAC and intravitreal chemotherapy injections, it will be interesting to evaluate the long term visual and orthoptic examination with these new treatments and hence the current report will serve as a baseline for the era of systemic chemotherapy.

In summary, following multimodality treatments for group D retinoblastoma patients and mean follow-up time of 64 months, final mean visual acuity was 20/283. Depending on age of presentation, tumour location in respect to the foveola and mainly whether adjuvant TTT was applied, final VA was better/worse than 20/200. At last visit, 60% of patients had

exotropia or esotropia and 22% had nystagmus. With the expectation of improved salvage rates for group D eyes, these results are useful information for clinicians, patients and patients' families.

ACKNOWLEDGEMENT

The authors indicate no funding support and no financial disclosures.

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FIGURE LEGEND

Figure 1 - Modified CONSORT (Consolidated Standards of Reporting Trials) Diagram showing the progress of patients through the study.

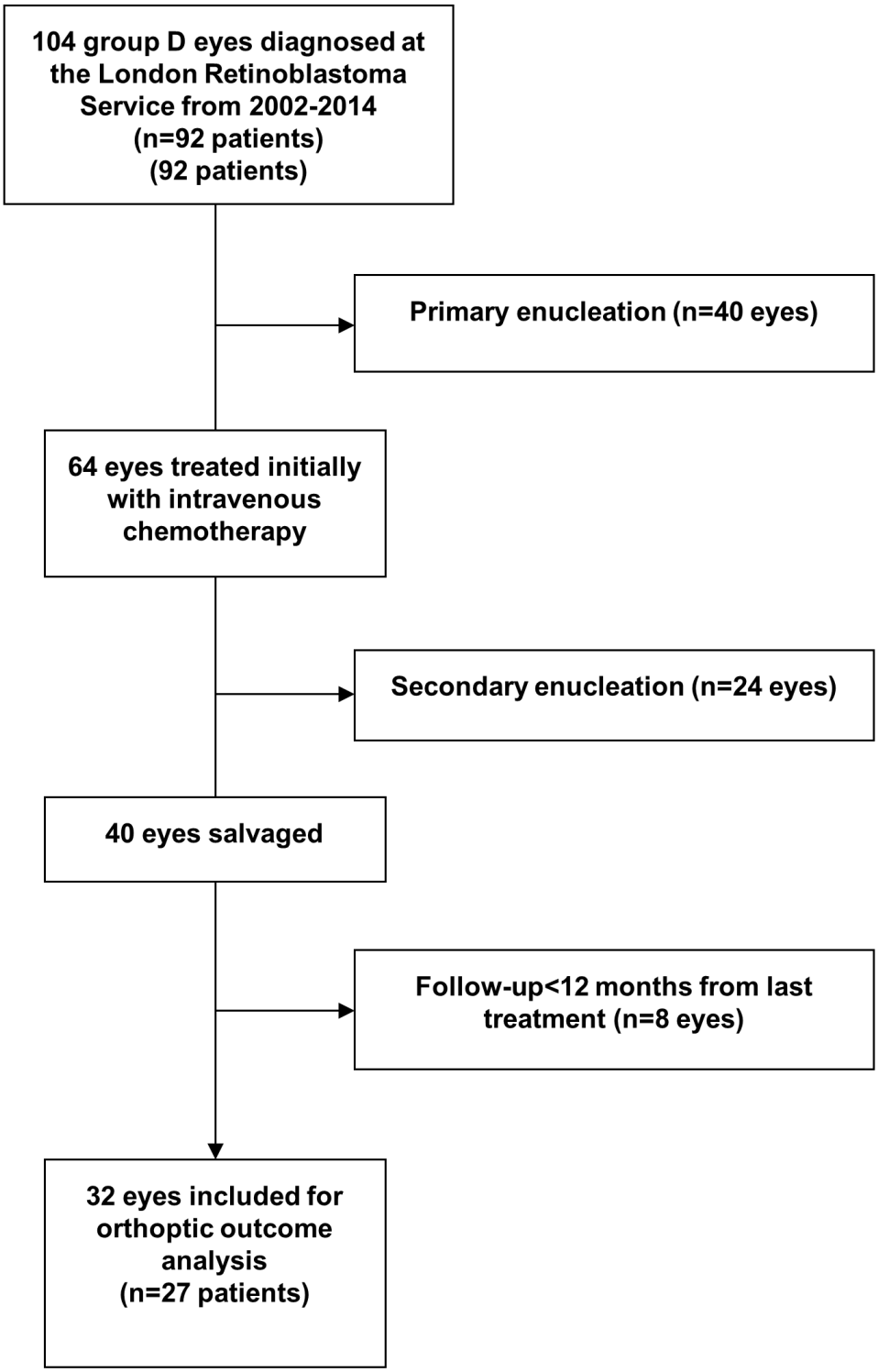

Table 1. Correlations to final logMAR vision equivalent in salvaged group D retinoblastoma eyes: univariate analysis

Parameter	Number (%)/mean ± std. error mean	Mean logMAR ± std. error mean	Significance
Demographics and genetics			
Gender			0.211
Male	14 (44)	1.36 ± 0.21	
Female	18 (56)	0.99 ± 0.20	
Age of presentation (months)	12.41 ± 1.75	NA	0.017
Family history of Rb			0.770
Sporadic	25 (78)	1.18 ± 0.16	
Familial	7 (22)	1.07 ± 0.40	
Germline disease			0.679
Genetic	25 (78)	1.19 ± 0.17	
Non-genetic	7 (22)	1.04 ± 0.33	
First clinical examination			
Laterality			0.464
Right eye	16 (50)	1.26 ± 0.22	
Left eye	16 (50)	1.04 ± 0.19	
Tumour elevation (mm)	9.16 ± 0.49	NA	0.337
Tumour base (mm)	11.43 ± 0.57	NA	0.982
Retinal detachment			0.495
Yes	26 (81)	1.11 ± 0.15	
No	6 (19)	1.37 ± 0.44	
Foveal Rb			0.002
Yes	23 (72)	1.42 ± 0.15	
No	9 (28)	0.47 ± 0.22	
Subretinal seeds			0.417
Yes	17 (53)	1.27 ± 0.17	
No	15 (47)	1.03 ± 0.25	
Vitreous seeds			0.057
Yes	14 (44)	0.84 ± 0.22	
No	18 (56)	1.40 ± 0.18	
Adjuvant treatments			
IAC			0.923
Yes	5 (16)	1.19 ± 0.40	
No	27 (84)	1.15 ± 0.16	
Plaque brachytherapy			0.102
Yes	5 (19)	0.60 ± 0.19	
No	27 (81)	1.26 ± 0.16	
TTT			0.026
Yes	18 (56)	1.44 ± 0.20	
No	14 (44)	0.79 ± 0.18	
Cryotherapy			0.072
Yes	24 (75)	1.00 ± 0.17	
No	8 (25)	1.61 ± 0.26	

Last visit examination and follow-up			
Tumour – foveola at last visit (mm)	1.94 ± 0.52	NA	0.003
Tumour – optic disc at last visit (mm)	2.00 ± 0.44	NA	0.369
Follow-up (months)	64.41 ± 6.76	NA	0.938
Last treatment – last follow-up (months)	50.70 ± 7.08	NA	0.700
Rb – retinoblastoma, IAC – intra-ophthalmic artery chemotherapy, TTT – transpupillary thermotherapy. NA – not applicable, as analysed as a continuous parameter.			

Table 2. Correlations to final logMAR vision equivalent in salvaged group D retinoblastoma eyes: multivariate analysis (Stepwise Linear Regression).

Parameter	Unstandardized Coefficients (β)	95% Confidence Interval for β	Significance
Age of presentation (mm)	-0.024	(-0.053)-0.004	0.093
Foveal Rb (yes vs. no)	0.363	(-0.559)-1.285	0.426
TTT (yes vs. no)	0.664	0.175-1.153	0.010
Tumour – fovea at last visit (mm)	-0.055	(-0.211)-0.101	0.475

Rb – retinoblastoma, TTT – transpupillary thermotherapy.

Table 3. Visual acuity, strabismus and nystagmus at final visit in 32 (27 patients) salvaged group D eyes following multimodality treatment.

Patient#	IIRC (R/L)	cTNMH* (R/L)	Age of presentation (months)	Presenting sign	Final logMAR R	Final logMAR L	Nystagmus	Strabismus
1	D/D	cT2bN0M0H1/cT2bN0M0H1	19.6	Leukocoria	0.9	Enucleated	Nil	NA
2	D/D	cT2bN0M0H1/cT2bN0M0H1	4.4	Leukocoria	1	1.1	Yes	Alt ET
3	D/D	cT2bN0M0H1/cT2bN0M0H1	2.5	Leukocoria	2.3	Enucleated	Yes	NA
4	B/D	cT1bN0M0H1/cT2bN0M0H1	14.8	Strabismus	0.08	1.3	Nil	LXT, LHoT, LIO u/a
5	E/D	cT3cN0M0H1/cT2bN0M0H1	9.9	Strabismus	Enucleated	0.7	Nil	NA
6	D/D	cT2bN0M0H1/cT2aN0M0H1	23.7	Strabismus	0.3	Enucleation	Nil	NA
7	D/D	cT2bN0M0H1/cT2bN0M0H1	4.6	Leukocoria	0.1	-0.2	Nil	RX(T)
8	0/D	cT0N0M0H0/cT2aN0M0H0	1.6	Leukocoria	-0.06	1.8	Nil	LXT
9	C/D	cT2bN0M0H1/cT2aN0M0H1	2.3	Leukocoria	0.1	1.8	Nil	Nil
10	D/C	cT2aN0M0H1/cT2bNoMoH1	10.8	Leukocoria + strabismus	2.6	0.02	Nil	Nil
11	D/E	cT2bN0M0H1/cT3cN0M0H1	17.7	Leukocoria + strabismus	0.88	Enucleated	Yes	NA
12	D/D	cT2bN0M0H1/cT2bN0M0H1	5.9	Leukocoria	1.2	1.2**	Yes	Alt XT
13	0/D	cT0N0M0H0/cT2bN0M0H0	12.6	Strabismus	0.04	1.12	Nil	LXT
14	0/D	cT0N0M0H0/cT2bN0M0H0	11.7	Leukocoria	0	2.08	Nil	LXT
15	D/D	cT2aN0M0H1/cT2aN0M0H1	11.4	Nystagmus	1.3	0.4	Yes	RXT
16	D/D	cT2bN0M0H1/cT2bN0M0H1	11.1	Strabismus	2.08	0.5	Nil	RXT
17	E/D	cT3bN0M0H1/cT2bN0M0H1	3.6	Leukocoria	Enucleated	1.38	Yes	NA
18	D/C	cT2bN0M0H1/cT2bN0M0H1	16.4	Strabismus	0.9	Enucleated	Nil	NA
19	D/A	cT2bN0M0H1/cT1aN0M0H1	1.9	Strabismus	2.6	0.1	Nil	RXT
20	0/D	cT0N0M0H0/cT2bN0M0H0	13.1	Leukocoria	0	1.78	Nil	LXT
21	0/D	cT0N0M0H0/cT2bN0M0H0	7.3	Leukocoria	0	0.26	Nil	Nil
22	D/D	cT2bN0M0H1/cT2aN0M0H1	19.3	Leukocoria	0.9	0.16	Nil	RET
23	D/0	cT2bN0M0H0/cT0N0M0H0	50.4	Leukocoria	0.1	0	Nil	Nil
24	D/0	cT2bN0M0H1/cT0N0M0H1	15.1	Leukocoria	0.62	-0.02	Nil	Nil
25	D/A	cT2bN0M0H1/cT1aN0M0H1	9.5	Leukocoria	2.6	0.2	Nil	RXT
26	0/D	cT0N0M0H1/cT2bN0M0H1	12.1	Strabismus	0	2.3	Nil	LXT
27	D/0	cT2bN0M0H0/cT0N0M0H0	32.9	Leukocoria + strabismus	0.14	-0.02	Nil	RET, RSO palsy, RHT

IIRC – International Intraocular Retinoblastoma Classification,[7] R – right, L – left, NA – non-applicable, Alt – alternate, ET – esotropia, XT – exotropia, HoT – hypotropia, IO – inferior oblique, u/a – under action, X(T) – intermittent exotropia, SO – superior oblique, HT – hypertropia.

* 8th edition AJCC/UICC clinical staging system.[24]

** Less than 12 months of follow-up since last treatment, hence not included for visual outcomes analysis.