Primary Intravenous Chemotherapy for Group D Retinoblastoma: A 13-Year Retrospective Analysis

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SYNOPSIS

Primary intravenous chemotherapy followed by adjuvant treatments as required for group D retinoblastoma resulted in the present study with an eye salvage rate of 63% and no cases of metastasis or death.

ABSTRACT

Background

Eye salvage rate for group D retinoblastoma using intravenous chemotherapy (IVC) as a primary modality is less than 50%. To report on 13-years' experience with the use of primary IVC for group D retinoblastoma.

Methods

A retrospective analysis of 64 group D eyes (52 patients) treated with primary IVC, from 2002-2014.

Results

The median age at presentation was 11.0 months (mean: 18.6, range: 0.6-144.0), 35 (67%) patients had bilateral disease, 38 (73%) germline disease and 8 (15%) cases were familial. In addition to IVC, patients received a median number of 3 treatments (mean: 6, range: 0-24), including thermotherapy/cryotherapy, plaque radiotherapy, intra-ophthalmic artery chemotherapy (IAC) and/or intra-vitreous chemotherapy. External beam radiotherapy was used in 5 eyes, all of which were eventually enucleated. In a median follow-up time of 55 months (mean: 64, range: 14-156) 63% of eyes were salvaged. By Kaplan-Meier survival analysis, globe salvage rate was 83%, 70%, 59% and 45% at 1, 3, 5 and 10 years, respectively. There were no cases of metastatic spread from intraocular retinoblastoma and no deaths. IVC-related adverse events included febrile neutropenia in 21 (40%) patients and anaphylactic reaction to carboplatin in 2 (4%), all conservatively resolved. Of the patients receiving IAC, 3rd and 6th nerve palsy was documented in 2 (10%) and 1 (5%) eyes, respectively.

Conclusions

Primary IVC for group D eyes, with adjuvant treatments as required, was found to be a safe and efficient approach, achieving 63% eye salvage rate, no metastatic spread from intraocular retinoblastoma and no deaths. IAC has now replaced EBRT as a successful salvage treatment.

INTRODUCTION

The treatment of intraocular retinoblastoma has advanced over the years and a wide range of options is available. Over the last 2 decades one of the major treatment options has been intravenous chemotherapy (IVC) and the classification of intraocular retinoblastoma has changed from the Reese-Ellsworth (R-E),[1] which predicted success from radiotherapy, to the International Classification of Retinoblastoma (ICRB),[2] which predicts success in the era of chemotherapy. In this schema, the most advanced cases, Group E, are usually enucleated and Groups A to C demonstrate over 90% chance of success of globe salvage using local treatments with IVC.[3] It is the Group D eyes that are the challenging cases in terms of eye salvage.

Since external beam radiotherapy (EBRT) was widely abandoned and IVC for intraocular retinoblastoma introduced, the latter has been the main primary treatment for group D eyes in many centres,[4] achieving up to 47% eye salvage rate.[3] With development and popularisation of intra-ophthalmic artery chemotherapy (IAC),[5,6] this treatment has found more recent favour as a primary treatment for group D eyes due to its selectivity and reported success in achieving tumour control, even being used in some centres for bilateral cases.[7] However, first line IAC has possible drawbacks, the most prominent of which relates to its selectivity for the eye, potentially allowing systemic spread.[8,9] In addition, as it is a modality requiring advanced infrastructure and expertise, it is not available in all centres.

In the London Retinoblastoma Service the primary treatment used for the majority of group D retinoblastoma patients has been IVC. Selected patients are treated by primary enucleation, but attempts to preserve the globe without compromise to patient survival are being increasingly favoured. In the UK, IAC is used mainly as a salvage treatment.

The goal of this study was to report on the management course and outcomes of group D eyes treated initially in our centre with IVC.

METHODS

This was a retrospective chart review of consecutive group D retinoblastoma cases, classified according to the ICRB,[2] that presented to the Retinoblastoma Service at the Royal London Hospital, from 27.11.2002 – 17.12.2014, and treated initially with IVC. The study was approved by the Barts Health NHS Trust institutional review board (number 6622).

Data retrieved from clinical notes included patients' age, gender, inheritance status (i.e. retinoblastoma family history), presenting signs, clinical variables, genetic analysis, treatment specifications and extraocular complications. Two of the authors (IDF and KCJ) examined all RetCam images, including fluorescein angiograms when available, of all patients, analysed the scans and recorded the results.

Cryotherapy, transpupillary thermotherapy (TTT) and ruthenium plaque brachytherapy were performed at the discretion of the treating clinician. For cryotherapy, a cryosurgical system (Mira, Waltham, MA, USA) was used, and each treatment session included 3 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. During the study period, overall 3 physicians treated the study patients, using the same treatment protocols. Decision to enucleate an eye or treat with chemotherapy was made after a joint consultation between the treating ophthalmologist/s and medical oncologist/s. Implants used after enucleations were vicryl mesh-coated hydroxyapatite, to which the extraocular muscles were attached, or acrylic, in which cases a myoconjunctival technique was used.[10] The presence of high risk features for systemic spread on histopathological evaluation[11] prompted treatment with adjuvant IVC. IVC for intraocular tumours included 6 courses of vincristine, etoposide and carboplatin (VEC), given via a central venous line, approximately every 3 weeks. In cases in which second-line IVC was indicated, or in cases of high risk features on histopathology in enucleated eyes, the protocol included ifosfamide, vincristine and doxorubicin (IVAd), given for 4-6 courses. The technique of intra-vitreous chemotherapy (IViC) was previously described and the agents used were melphalan and/or topotecan.[12] For IAC, the agents used were melphalan, topotecan and/or carboplatin, and the technique has been described by our centre previously.[13]

Statistical Analysis and Study Definitions

All calculations were performed using Microsoft Excel 2013 software (Microsoft Corporation, Redmond, WA) and SPSS software version 17.0 (SPSS, Inc., Chicago, IL). P-values were calculated using Chi-squared function and T-Test, and survival estimates using Kaplan-Meier analysis. Early treatment failure was defined as insufficient tumour response (main tumour and/or seeds), requiring change in management, during or immediately after IVC cycles.

RESULTS

Patient characteristics and clinical presentation

There were 104 group D retinoblastoma eyes of 92 patients diagnosed and managed in our service during the study period. Of these, 40 (37.5%) underwent primary enucleation. The remaining 64 eyes of 52 patients (28 (54%) males) were treated by means of primary IVC and these comprise the present study cohort. The presentation details and genetic analysis of the study patients are summarised in **Table 1** and results of clinical examination at presentation in **Table 2**.

Table 1. Demographics, variables at presentation and genetic analysis of 52 Group D retinoblastoma patients (64 eyes) treated by primary intravenous chemotherapy.

Parameter	N=52 patients[a]	%
Gender		
Male	28	54
Female	24	46
Presenting signs		
Leucocoria	29	56
Strabismus	13	25
Leucocoria and strabismus	4	8
Other[b]	6	12
Uni/bilateral retinoblastoma		
Unilateral at presentation (at final follow-up)	18 (17)	35 (33)
Bilateral at presentation (at final follow-up)	34 (35)	65 (67)
Contralateral eye's classification in bilateral cases (n=35)		
0[c]	1	3
A	5	14
B	6	17
C	5	14
D	12	34
E	6	17
Age first symptoms noticed (months)[d]		
Median (mean, range)	9.0 (17.1, 0.1-142.0)	
Age at diagnosis (months)		
Median (mean, range)	All cohort 11.0 (18.6, 0.6-144.0) Unilateral cases 14.0 (31.6, 1.5-144.0) Bilateral cases 10.0 (12.3, 0.6-108.0)	
Presumed diagnosis made locally – final diagnosis (days)		
Median (mean, range)	6.0 (5.7, 1.0-36.0)	
Genetics and inheritance		
Blood mutation found in	38	73
Sporadic	44	85
Unilateral	16	36
Bilateral	28	64
Familial	8	15
Unilateral	1	12.5
Bilateral	7	87.5

Trilateral[e]	1	12.5

[a] Data presented for the whole cohort, unless otherwise stated.
[b] Other presenting signs included periorbital swelling in one patient, floaters and flashing lights in 3 children >8-year old and nystagmus in 2 patients.
[c] A familial case that presented as D/0, however developed new tumours in the non-D eye nearly 8 months after first presentation.
[d] Retrospectively reported by the parents/guardians.
[e] Bilateral disease plus pinealblastoma.

Table 2. Clinical examination at presentation of 64 Group D retinoblastoma eyes (52 patients) treated by primary intravenous chemotherapy.

Parameter	**N=64 eyes**	**%**
Laterality		
Right eye	40	63
Left eye	24	38
Horizontal corneal diameter of the D eye (mm)		
Median (mean, range)	11.5 (11.4, 10.0-12.5)	
Tumour focality		
Unifocal	41	64
Multifocal	23	36
Tumour dimensions (mm)		
Median (mean, range)	Height: 9.7 (10.1, 4.4-19.2) Base: 13.0 (12.6, 7.8-19.0)	
Quadrants of retinal detachment		
No detachment	6	9
Local	12	19
1	3	5
2	7	11
3	7	11
4	29	45
Optic disc obscured		
Not obscured	17	27
Obscured	47	73
Fovea involvement		
Not involved	11	17
Sub-foveal fluid	11	17
Foveal tumour	42	66
Retinoblastoma seeds		
No seeds	9	14
Sub-retinal	41	64
Vitreous	28	44
Both	14	22

Leucocoria was the most common presenting feature (56%), followed by strabismus (25%). Of the 52 study patients, 34 (65%) presented with bilateral retinoblastoma and the

remaining 18 (35%) with unilateral disease. One familial case that presented as unilateral Group D retinoblastoma later developed retinal tumours in the non-D eye. Of the bilateral cases, bilateral D was the most common combination (34%).

The median age of diagnosis was 11.0 months (mean: 18.6, range: 0.6-144.0). Eight patients (15%) had positive family history, 1 (12.5%) of which presented with trilateral retinoblastoma. On genetic analysis, available approximately 3 months after first diagnosis, in 38 patients (73%) a blood *RB*1 mutation was found.

Multifocal tumours were found in 23 (36%) eyes, a total retinal detachment in 29 (45%) eyes, the optic disc was obscured in 47 (73%) eyes, foveal tumour involvement in 42 (66%) eyes and retinoblastoma seeds, subretinal and/or vitreous, were detected in 55 (86%) eyes, in ≥97% eyes seeds were spread in a diffuse manner.

Management and outcomes

Table 3 summarizes the management course of the study patients. Of the bilateral cases, there were 6 that presented with group D in 1 eye and group E in the fellow eye. All of these had the group E eye enucleated and histology evaluated prior to commencing IVC.

Table 3. Management summary of 64 Group D retinoblastoma eyes (52 patients) treated with primary intravenous chemotherapy.

Parameter	Number=64 eyes	%
Primary intravenous chemotherapy regimen [a]		
Number of treatments		
Median (mean, range)	6 (6, 2-6)	
Time range (days)		
Median (mean, range)	120 (123, 33-160)	
Early treatment failure (no response to chemotherapy)	8	12.5
Total number of additional treatments [b]		
Median (mean, range)	3 (6, 0-24)	
Number of eyes having additional treatments		
No additional treatments	3	5
Additional diode laser and/or cryotherapy	50	78
During systemic chemotherapy courses	23	46
Ruthenium plaque radiotherapy	12	19
Intra-ophthalmic artery chemotherapy	20[c]	31
Median number of treatments (mean, range)	3 (3, 1-6)	
Intravitreal chemotherapy	4[d]	6
Median number of treatments (mean, range)	2 (3, 1-6)	
Second line systemic chemotherapy	2	3
External beam radiotherapy	5	8

[a] Vincristine, etoposide, carboplatin.
[b] Including diode laser, cryotherapy, plaque radiotherapy and salvage intravenous chemotherapy, excluding external beam radiotherapy and secondary enucleation.
[c] First patients treated in 2009.
[d] First patient treated in 2014.

Standard protocol of 6 cycles of intravenous VEC was used in all patients, except 3, whose tumours failed to respond to IVC. Of these, 2 were switched to IAC, but underwent enucleation after 2 treatments due to further tumour progression, and one was enucleated after 5 VEC cycles.

Altogether, early treatment failure occurred in 8 (12.5%) eyes, 5 of which underwent secondary enucleation immediately after completion of the 6th IVC cycle. On statistical analysis, tumour focality and horizontal corneal diameter of the D eye were the only variables associated with early treatment failure (**Table 4**). In detail, 100% of eyes with multifocal retinoblastoma showed good response to primary IVC compared to 81.5% of eyes with unifocal tumours (p=0.043), and larger horizontal corneal diameter was found to associate with higher chances for early treatment failure (p=0.012). Of note, in no case was a difference found in corneal horizontal diameter between eyes of the same patient.

Table 4. Primary intravenous chemotherapy in 64 group D eyes of 52 patients: favourable response versus early treatment failure.

Parameter	Favourable response (56 eyes of 45 patients, %)	Early treatment failure[a] (8 eyes of 7 patients, %)	*P*
Gender			0.107
Male	22 (49)	6 (86)	
Female	23 (51%)	1 (14)	
Presenting signs			0.583
Leucocoria	26 (58)	3 (43)	
Strabismus	10 (22)	3 (43)	
Leucocoria and strabismus	4 (9)	0 (0)	
Other[b]	5 (10)	1 (14)	
Laterality			0.699
Right eye	34 (61)	6 (75)	
Left eye	22 (39)	2 (25)	
Age at diagnosis (months)			0.257
Median (mean, range)	11.0 (15.4, 0.6-108.0)	24.0 (39.0, 3.0-144.0)	
Horizontal corneal diameter of the D eye (mm)			0.012
Median (mean, range)	11.0 (11.3, 10.0-12.5)	12.0 (12.0, 11.5-12.5)	
Tumour focality			0.043
Multifocal	33 (59)	8 (100)	
Unifocal	23 (41)	0 (0)	
Tumour dimensions (mm)			
Median (mean, range)	Height: 9.3 (9.9, 4.4-19.2) Base: 12.2 (12.3, 7.8-19.0)	Height: 12.4 (12.6, 11.5-13.9) Base: 14.4 (14.7, 14.1-15.5)	0.598 0.671
Retinal detachment			1.000
Detached	50 (89)	8 (100)	
Not detached	6 (11)	0 (0)	
Optic disc obscured			0.670
Obscured	40 (71)	7 (88)	
Not obscured	16 (29)	1 (13)	

Fovea involvement			0.837
Sub-foveal fluid	10 (18)	1 (13)	
Foveal tumour	36 (64)	6 (75)	
Not involved	10 (18)	1 (13)	
Retinoblastoma sub-retinal seeds			1.000
Present	36 (64)	5 (63)	
Not present	20 (36)	3 (38)	
Retinoblastoma vitreous seeds			1.000
Present	25 (45)	3 (38)	
Not present	31 (55)	5 (63)	
[a] Defined as no regression of the intraocular tumour components (main tumour and/or seeds), during or immediately after systemic chemotherapy cycles, requiring change in management.			

Of the 64 eyes treated with IVC, 95% required additional treatments, mainly in the form of TTT and/or cryotherapy. Additional chemotherapy treatments included IAC in 20 (31%) eyes, IViC in 4 (6%) eyes and second line IVC in 2 (3%). Five (8%) were treated with lens-sparing EBRT; however all eventually had to undergo secondary enucleation (in 4 (80%) cases the underlying reason was uncontrolled tumours and in 1 (20%) development of iris neovascularization and non-clearing vitreous haemorrhage).

The median follow-up time for the whole cohort was 55 months (mean: 64, range: 14-156), in which time 40 (63%) eyes were salvaged. The median time from last intervention to last follow-up visit was 24 months (mean: 38, range: 0-156). Kaplan-Meier survival analysis showed an overall globe salvage rate of 83%, 70%, 59% and 45% at 1, 3, 5 and 10 years, respectively. **Figure 1** shows the cumulative eye-survival according to Kaplan-Meier analysis, and in addition a sub-analysis of eyes that resulted with early treatment failure and those treated with salvage IAC. On statistical analysis, none of the clinical variables emerged as significant risk factors for secondary enucleation. Of the 24 enucleated eyes, 11 (46%) had been treated with salvage IAC, but IAC was not found to be a significant risk factor, nor a protective one, for secondary enucleation (p=0.118). Of the 4 eyes treated with IViC, only one underwent secondary enucleation.

Of the 24 secondary enucleations, 42% were performed during the first year of follow-up, 58% after the 1st year, 38% after the 2nd year and 25% after the 3rd year. Indications for secondary enucleation included tumour relapse at the optic nerve head, neovascularization of the iris with vitreous haemorrhage, tumour relapse in the anterior chamber, multiple subretinal/vitreous seeds with/without subtotal/total retinal detachment. Most cases showed a combination of these indications. Six (25%) secondary enucleations were performed before IAC was available and the rest (75%) after. To note, 20 (31%) eyes presented before 2009, i.e. first IAC use, however all were further followed-up during the period that IAC was available, and in 4 (20%) of this early cohort, IAC was used. Of the 22 patients (42%) that underwent secondary enucleation, 4 (8%) who had bilateral retinoblastoma, eventually underwent bilateral enucleation.

Of the 24 secondary enucleated eyes, 5 (21%) showed high-risk features on histopathology and were treated with adjuvant IVC because of risk of secondary spread.

Extraocular-related adverse events

IVC related adverse events included Grade 3 febrile neutropenia in 21 (40%) patients and Grade 3 anaphylaxis after carboplatin administration in 2 (4%). IAC related adverse events included 3rd and 6th nerve palsies in 2 (10%) and 1 (5%) patients, respectively. In all of these cases, conservative management or observation resulted with complete resolution. In 2 (10%) cases IAC was abandoned due to technical difficulties in catheterization. No complications or related adverse events were recorded after IViC.

No case of metastatic spread from intraocular retinoblastoma and no cases of death occurred during the study period. However, 1 case with trilateral disease was also treated for pinealoblastoma that had metastasised to the spine, and was alive at the end of this study period.

DISCUSSION

The last 3 decades have witnessed huge developments in the management of retinoblastoma, with several new modalities becoming available. This has necessitated a rethink of the classification of intraocular disease from the R-E classification that predicted globe salvage in the era of EBRT,[1] to the ICRB, which was developed in the era of chemotherapy.[2] The present study bridges an era in our centre after the establishment of IVC for retinoblastoma,[4,14–16] when EBRT was used for salvage, to the emergence of IAC for salvage. This was a large cohort of 64 group D eyes followed-up for a median time of nearly 5 years with an eye salvage rate of 63%. This is significantly higher than previous similar studies.[3,17–25] Before IAC, Shields et al. reported a globe salvage rate of 47% in group D eyes treated by primary IVC,[3] the highest success rate achieved in the pre-IAC era. Of note, Shields et al. used the Philadelphia version of the IRCB,[3] whereas we used slightly different criteria to define D eyes, according to the Children's Hospital Los Angeles scheme,[2] and it was shown that such discrepancies may adversely impact attempts to compare treatment outcomes.[26] Nevertheless, this does not fully explain the disparity in salvage rates between the 2 studies.

In a previous study from 1995-2003 from our centre on group D heritable retinoblastoma treated with primary IVC with median follow-up of 30 months, found that 11/18 eyes (61%) were salvaged, with 5 eyes requiring salvage with EBRT.[23] Since then, the role of EBRT has been relegated to being akin to treatment failure, especially with increased risk of second cancers in patients with germline retinoblastoma.[27] Interestingly, in the present study, salvage EBRT was used in 5 eyes, all in the early cases, prior to the use of IAC, and in all, treated eyes were eventually enucleated. Presumably, the longer follow-up in this report allowed for more definitive outcomes. These findings, in addition to the known risk associated with EBRT,[27] strengthen the approach that EBRT should have a diminished role in treating intraocular retinoblastoma.

IAC and more recently IViC injections are important adjuncts and are important in achieving the relatively high salvage rate in the present cohort. Interestingly, neither was found to be a significant protective factor for eye salvage. As for IViC, this is not surprising, as it was first used in the current cohort in 2014 and only in 4 eyes. IAC however was first introduced in 2009 and used in 20 eyes in this study. A reasonable explanation would be that IAC was used as a salvage treatment initially in more resistant cases, and 11 of these had to undergo secondary enucleation.

Yousef et al., in a systematic review on IAC, reported a total of 67% success rate, when used as second line therapy, but for all eye groups,[8] clearly different to the present study that concentrates on D eyes only. Eye salvage for advanced retinoblastoma in their analysis was found to be 57%, when IAC was used as first and second line and for ICRB groups D and E.[8] Shields et al. reported 67% eye retention in a small case series of 6 D eyes treated with primary IVC followed by IAC.[28] Abramson et al. recently published their results on D eyes treated with first line IAC (n=47) and reported on 85.1% success rate.[9] In their study the median follow-up time was 30 months, in 12 (24%) eyes it was under a year, and in 7 (14%) 2-6 months. In our study nearly 60% of secondary enucleations were performed after the first year of follow-up and nearly 40% after the second year, so it is possible that later relapse might lead to more enucleations and a lower overall globe salvage. Conversely, it is

possible that we may be able to increase our globe retention rates by earlier use of salvage IAC, as our initial cases were treated with this modality as a last resort. Overall then, results from the present and other studies show that IAC, when indicated, is a powerful tool as an adjunct to primary IVC for group D retinoblastoma, enabling retention of a greater number of eyes compared to IVC alone or with the use of additional local consolidation.

We tried to understand whether certain features would sub-classify Group D into eyes that were more likely to succeed with IVC or would be higher risk for enucleation. None of the variables emerged as significant risk factors for secondary enucleation. This is not surprising, as per definition, D eye tumours hold common features, including tumour size and the presence of retinal detachment and seeding. To note, in 2 relatively large cohort studies on retinoblastoma eyes treated by primary IVC,[20,29] group D eyes were analysed as part of a larger cohort containing additional ICRB groups and no sub-analysis was performed. In the literature, there are no reports of specific risk factors for secondary enucleation of D eyes treated initially with IVC.

Eight eyes resulted with early treatment failure and eventually secondary enucleation. Salvage IAC was not available for all, but when used for 2 of these cases, it also failed to achieve a beneficial effect. There is only scant literature on retinoblastoma that does not respond to IVC and that necessitates immediate change in management. In a retrospective analysis by Gunduz et al.,[30] unresponsive disease was defined as persistence of retinal tumours, vitreous or subretinal seeds after the second IVC cycle, with no appreciable sign of regression. Recurrent disease was defined as regrowth of tumours any time after an initial favourable response. Of 105 eyes (all R-E classification groups) 10 (10%) eyes were unresponsive to treatment. On statistical analysis, however, unresponsive cases were combined with recurrent ones, precluding specific insight into the former subgroup. Interestingly, in the present study, eyes with unifocal tumours and those with relatively larger horizontal corneal diameters (in both eyes) were found to be at significant risk for early treatment failure. We have no reasonable explanations for these associations. It should also be mentioned, that detection of numerous tumours, usually in cases of genetic disease, is not always possible, especially in D eyes, as in most a total retinal detachment can limit a clear view and ultrasound is only partially helpful in such cases.

In 3 eyes (5%) no additional treatments to IVC were needed in order to reach tumour control and in more than half TTT and/or cryotherapy were given after completion of the chemotherapy cycles. There is no consensus on the use of adjuvant therapies. In some reports routine use of consolidating local modalities was superior to chemotherapy alone,[31] but caution is sometimes necessary in case of adverse impact.[32,33] This argues for adjuvant treatments given only when indicated, as they may also have an adverse impact on the treated eyes.

The extraocular complications and adverse events related to IVC reported in this study are in the spectrum found in the literature.[34] This is also the case regarding IAC.[13] For both modalities no serious or life-threatening events were recorded, but twice there was an anaphylactic reaction to systemic carboplatin that responded to conservative management.

Metastatic disease from intraocular retinoblastoma did not occur in any of the cases, an inherent protective feature of IVC over primary IAC.[8] The high globe retention rates reported with primary IAC for group D retinoblastoma (85%) are impressive, but there was a

6% metastatic rate in that study.[9] In the IVC era metastatic rates have been low, so the metastatic risks of primary IAC may temper the enthusiasm for this technique in some centres.

Limitations of this study include mainly its retrospective and non-randomized design. Nearly 40% of eyes during the study period underwent primary enucleation (hence were excluded from this analysis of chemotherapy treated eyes). This could potentially result in selection bias if the more advanced group D eyes were enucleated. Although not the subject of the current report, we compared the the primary enucleation with the primary IVC cohort (data not shown), and found that the enucleation cases were selected not for more advanced or complicated disease, but rather older age of presentation and usually unilateral disease. These reservations should be taken into account when interpreting the results of the present study. Additional limitations are inherent to the clinical examination of group D retinoblastoma eyes and include, in some cases, difficulty in assessing the number of tumours and the presence of subretinal seeds in case of a large retinal detachment. In regard to insufficient tumour response cases, the definite criterion to be included in this subgroup was change in management during or immediately after IVC. There are several tumour features that can change in respond to treatment and these include, among others, size, colour, vascularization, degree of calcification, number of tumours, and density. It is the combination of all of the above features summed-up on clinical examination that dictates whether change of management is required.

In summary, in this large cohort of group D retinoblastoma eyes, primary intravenous chemotherapy, followed by additional local therapies, tailored as per clinical need, was found to be an efficient and safe approach, achieving an eye salvage rate of 63% in a median follow-up time of nearly 5 years. In this time period no case of metastatic spread from intraocular retinoblastoma was recorded and no cases of death. These results are an improvement on those reported previously for group D eyes treated with primary intravenous chemotherapy, and are partly a result of IAC, that was added as a salvage modality, replacing EBRT. With the recent addition of IViC, both locally-delivered chemotherapy modalities, used as powerful adjuncts to primary intravenous chemotherapy, are expected to further improve eye salvage rates and control of the disease, replacing the use of EBRT.

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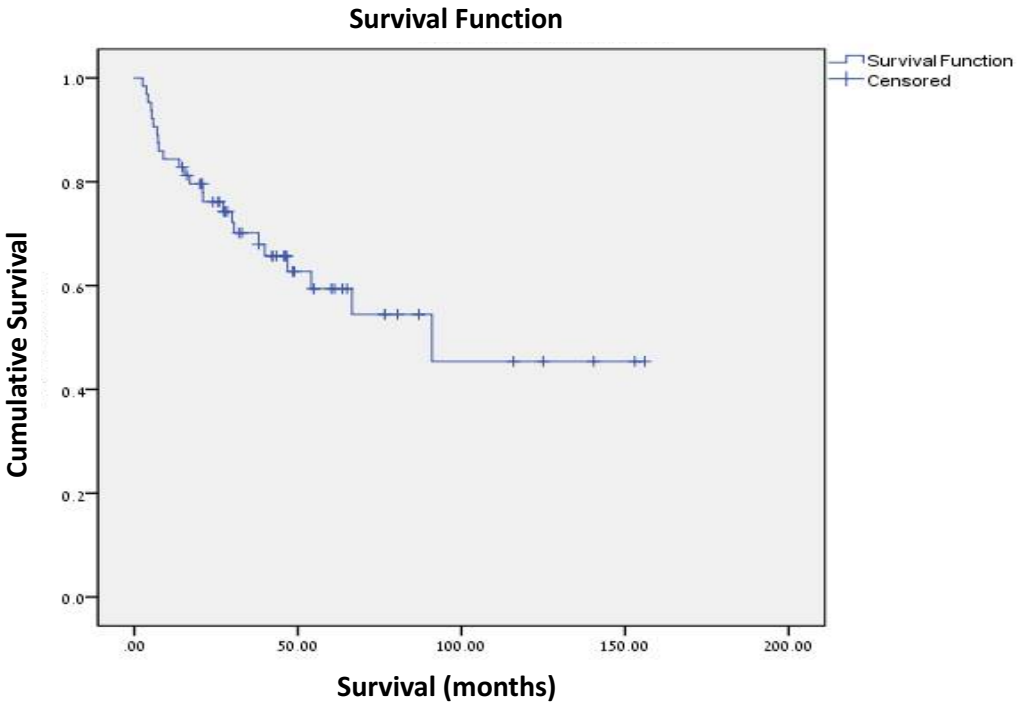
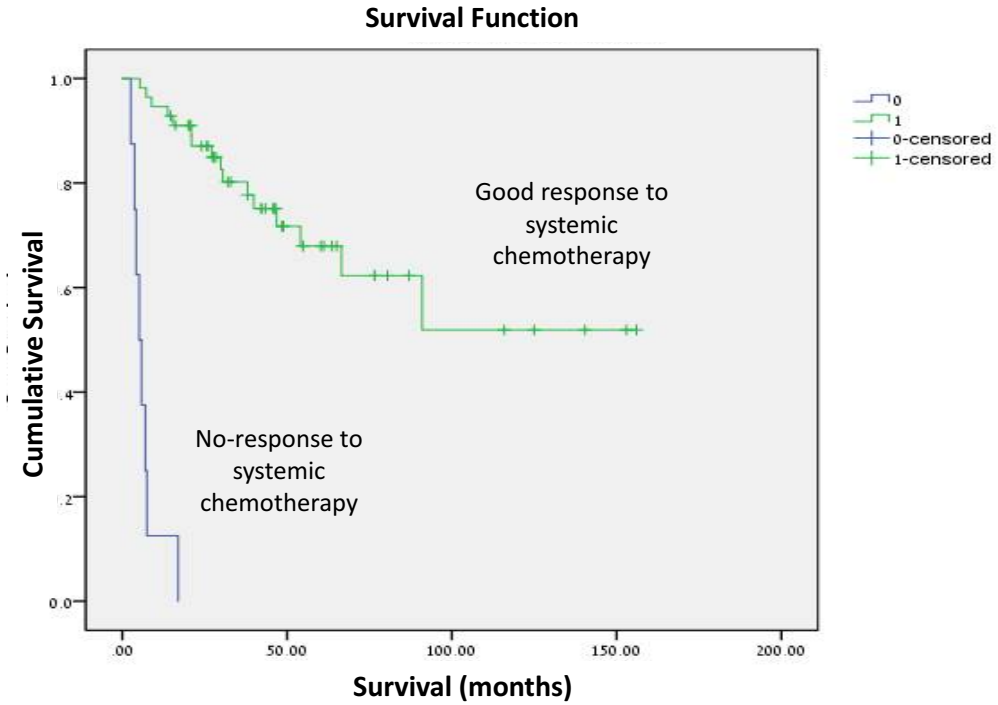
FIGURE LEGEND

Figure 1 – Kaplan-Meier estimates of globe salvage in (A) the whole cohort, (B) favourable initial response to primary intravenous chemotherapy (IVC) versus early treatment failure and (C) primary IVC versus primary IVC and salvage intra-ophthalmic artery (IAC).

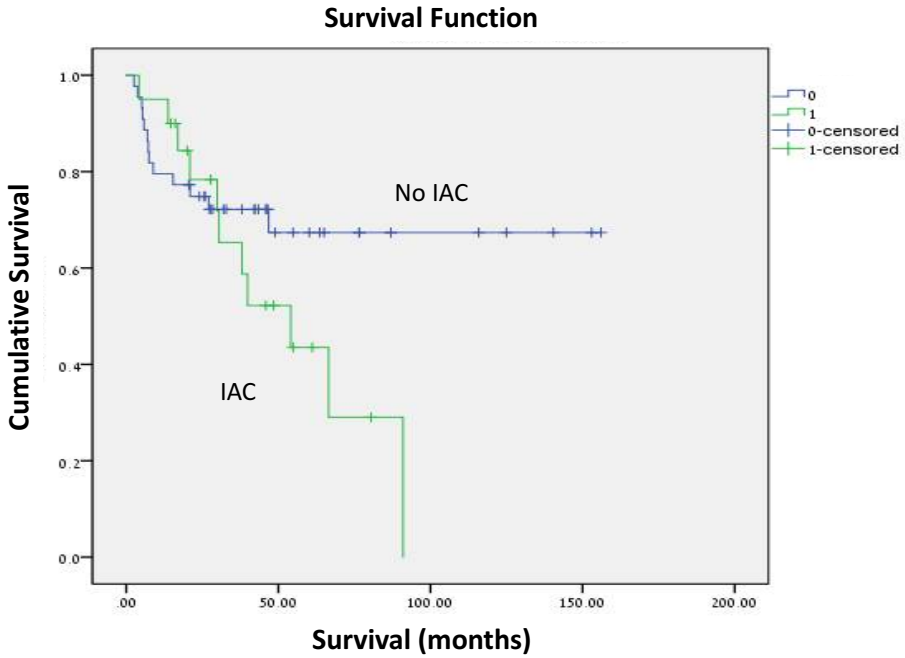
A



B


Survival Function
Cumulative Survival
1.0
.8
.6
.4
.2
0.0
.00
50.00
100.00
150.00
200.00
Survival (months)
Good response to systemic chemotherapy
No-response to systemic chemotherapy
0
1
0-censored
1-censored

C


Survival Function
Cumulative Survival
1.0
0.8
0.6
0.4
0.2
0.0
.00
50.00
100.00
150.00
200.00
Survival (months)
No IAC
IAC
0
1
0-censored
1-censored