Unilateral Retinoblastoma Managed With Intravenous Chemotherapy Versus Intra-Arterial Chemotherapy. Outcomes Based on the International Classification of Retinoblastoma

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Purpose: The objective of this study was to compare outcomes after intravenous chemotherapy (IVC) versus intra-arterial chemotherapy (IAC) for unilateral retinoblastoma.

Design: A retrospective comparative interventional case series.

Methods: Patients with unilateral retinoblastoma managed with either IVC using vincristine, etoposide, and carboplatin or IAC using melphalan with or without topotecan with a minimum of 1-year follow-up were compared. The primary outcome measure was globe salvage.

Results: Of 91 patients with unilateral retinoblastoma, IVC was employed in 42 (46%) cases and IAC in 49 (54%). By comparison (IVC vs IAC), patients in the IAC group had greater mean tumor diameter (14 vs 18 mm, $P < 0.001$) and thickness (7 vs 10 mm, $P = 0.001$), greater percentage with active vitreous seeds (29% vs 55%, $P = 0.01$), and greater total retinal detachment (10% vs 43%, $P < 0.001$). There were no cases of group A in either treatment arm. Globe salvage was not significantly different in groups B, C, or E, but there was significantly improved globe salvage with IAC for group D (48% vs 91%, $P = 0.004$). Control was significantly better with IAC for solid tumor (62% vs 92%, $P = 0.002$), subretinal seeds (31% vs 86%, $P = 0.006$), and vitreous seeds (25% vs 74%, $P = 0.006$). There were no patients with pinealoblastoma, second cancer, metastasis, or death in either group.

Conclusions: For unilateral retinoblastoma, IAC provided significantly superior globe salvage compared with IVC for group D eyes. In addition, IAC provided significantly superior control for solid tumor, subretinal seeds, and vitreous seeds.

Key Words: retinoblastoma, intravenous chemotherapy, intra-arterial chemotherapy, chemoreduction

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Over the past 20 years, retinoblastoma management has witnessed a major shift in conservative therapy from radiotherapy to chemotherapy.[1–5] In the mid-1990s, intravenous chemotherapy (IVC, chemoreduction) was introduced with an unexpectedly high tumor control and globe salvage rate of more than 90% in eyes with minimal to moderate tumor [International Classification of Retinoblastoma (ICRB) groups A, B, and C] and approximately 50% for those with more advanced tumor (group D).[6–10] Enucleation has remained an important treatment for the most extreme retinoblastoma (group E) with massive intraocular disease, vitreous hemorrhage, secondary glaucoma, or eyes at risk for metastatic disease.[2,11] In the mid to late 2000s, superselective intra-arterial chemotherapy (IAC) was introduced for retinoblastoma management.[12–15] This modality was immediately found capable of controlling eyes with relatively advanced tumor that previously might have required enucleation.[16,17]

For the past 22 years we have employed IVC, and in the past 8 years we have used IAC in the management of retinoblastoma. There remains debate on which therapy is most suitable for unilateral and bilateral retinoblastoma.[18] Herein, we analyze our single-institution experience, comparing IVC versus IAC as primary therapy for unilateral retinoblastoma based on the ICRB.

MATERIALS AND METHODS

Patient Data

The medical records of all patients diagnosed with unilateral retinoblastoma and treated at the Ocular Oncology Service of Wills Eye Hospital, Thomas Jefferson University, from January 1994 to June 2013 were retrospectively analyzed. Wills Eye Hospital Institutional Review Board approval was obtained, and the study adhered to the tenets of the Declaration of Helsinki. Inclusion criteria included only patients with unilateral retinoblastoma referred for primary management. The selected management included primary IVC or primary IAC. In general, IVC was used before 2008, and IAC after 2008, when it became available. Patients were excluded if treatment was initiated elsewhere before referral to the Ocular Oncology Service of Wills Eye Hospital and if previous treatment with laser photocoagulation, thermotherapy, cryotherapy, plaque radiotherapy, chemotherapy, or external beam radiotherapy was performed before our evaluation.

Among 1700 patient charts reviewed during this period, there were 91 cases of unilateral retinoblastoma suitable for inclusion and treated primarily with IVC (n = 42 eyes) or IAC (n = 49 eyes). Data were collected regarding patient demographics, clinical features, treatment methods, and treatment outcomes. Patient demographics included age at presentation, race, sex, eye involved, and family history of retinoblastoma. Clinical features included number of tumors per eye, tumor location, largest basal diameter (mm) and thickness (mm), presence of anterior chamber, subretinal or vitreous seeds and extent of seeding, associated retinal

detachment, extent of retinal detachment, and iris, retinal, or vitreal neovascularization. Basal diameter was measured by indirect ophthalmoscopy and thickness by ultrasonography. Each eye was classified according to the ICRB.[19,20]

Treatment Data

The treatment parameters included route of chemotherapy (IVC, IAC), chemotherapy medications and dose, and number of cycles. Our protocols for IVC and IAC have been previously published.[9,15] Regarding IVC, the regimen included vincristine (0.05 mg/kg), etoposide (5 mg/kg), and carboplatin (18.6 mg/kg) given on day 0 and etoposide (5 mg/kg) given again on day 1 for a total of 6 monthly cycles. In some advanced cases, slightly elevated etoposide (6 mg/kg) was used.[20] After the initial tumor reduction and resolution of subretinal fluid subsequent to the first or second cycle of IVC, local tumor consolidation with transpupillary thermotherapy or cryotherapy was provided. Regarding IAC, transfemoral artery catheterization was performed under general anesthesia and sterile conditions in the operating room as an outpatient procedure, and a 450-μm microcatheter was passed up to the ostium of the ophthalmic artery for delivery of melphalan (3, 5, or 7.5 mg), with or without topotecan (1 mg) or carboplatin (30 mg), diluted in 30 mL of saline in a pulsatile, nonlaminar infusion technique for a period of 30 minutes to maximize homogeneous drug delivery. When more than 1 drug was used, each was delivered separately for a period of 30 minutes. Intraoperative anticoagulation with heparin followed by oral aspirin (40 mg) for 2 weeks was given to all patients after IAC.

Outcomes

The primary outcome of the study was the rate of globe salvage after IVC versus IAC. Secondary outcomes included tumor control for solid tumor, subretinal seeds, and vitreous seeds, and the rates of treatment complications, secondary cancers, distant metastasis, and patient death. Tumor control was defined as complete tumor regression without the need for enucleation or external beam radiotherapy.

Statistical Evaluation

The patient demographics and tumor features of the IVC and IAC groups were compared using χ^2 testing to detect significant differences. The outcomes from each group were evaluated using the 2-tailed Fisher exact test for categorical data. For continuous variables, the Shapiro-Wilk test and the nonparametric Mann-Whitney *U* test were employed. *P* values of 0.05 or lower were considered statistically significant.

RESULTS

There were 91 patients with unilateral retinoblastoma included in this analysis and treated with IVC (n = 42 eyes) or IAC (n = 49 eyes). The patient demographics are listed in Table 1. A comparison of IVC and IAC revealed that the IAC group had older mean patient age (13 vs 22 months, $P = 0.001$), fewer whites (83% vs 60%, $P = 0.02$), more Asians (2% vs 16%, $P = 0.035$), and more common somatic mutation (24% vs 70%, $P < 0.001$). Regarding globe classification (IVC vs IAC), there was no significant difference in the frequencies of group B, C, and D eyes, but there were significantly more eyes with group E in the IAC group (7% vs 43%, $P < 0.001$).

The tumor features are listed in Table 2. A comparison of tumor features (IVC vs IAC) showed significant differences, with those in the IAC group demonstrating larger mean basal diameter (14 vs 18 mm, $P < 0.001$), greater thickness (7 vs 10 mm, $P = 0.001$), greater number of eyes with active vitreous seeds

TABLE 1. Patient Demographics

Feature	IVC, n (%) (n = 42 eyes)	IAC, n (%) (n = 49 eyes)	*P*
Mean (median, range) age at diagnosis, mo	13 (8, 1–79)	22 (19, 1–83)	0.001
Race			0.071
White	35 (83)	29 (60)	0.021
African American	2 (5)	6 (12)	0.279
Hispanic	4 (10)	5 (10)	1.000
Asian	1 (2)	8 (16)	0.035
Middle Eastern	0 (0)	1 (2)	1.000
Sex			
Male	28 (67)	24 (49)	0.137
Female	14 (33)	25 (51)	
Family history of retinoblastoma	7 (17)	2 (4)	0.075
Genetic testing			<0.001
Germline	7 (17)	8 (16)	1.000
Somatic	10 (24)	34 (70)	<0.001
Unavailable	25 (59)	7 (14)	<0.001
Study eye			0.211
Right	23 (55)	20 (40)	
Left	19 (45)	29 (60)	
ICRB			<0.001
Group A	0 (0)	0 (0)	1.000
Group B	7 (17)	2 (4)	0.075
Group C	7 (17)	4 (8)	0.334
Group D	25 (59)	22 (45)	0.208
Group E	3 (7)	21 (43)	<0.001

TABLE 2. Tumor Features

Feature	IVC, n (%) (n = 42 eyes)	IAC, n (%) (n = 49 eyes)	*P*
Main tumor features			
Mean (range) no. tumors	1 (1, 1–4)	1 (1, 1–2)	0.111
Eyes with multifocal tumors	4 (10)	1 (2)	0.177
Mean (median, range) largest diameter, mm	14 (14, 4–24)	18 (20, 8–25)	<0.001
Mean (median, range) thickness, mm	7 (7, 1–14)	10 (10, 4–18)	0.001
Subretinal seed features			
Active subretinal seeds	22 (52)	30 (61)	0.406
Mean (median, range) clock hour involvement	3 (1, 0–12)	4 (2, 0–12)	0.307
Location			0.222
Superior	0 (0)	1 (3)	1.000
Inferior	15 (68)	13 (44)	0.236
Temporal	1 (5)	0 (0)	0.462
Nasal	2 (9)	4 (13)	0.683
Diffuse (12 clock h)	4 (18)	12 (40)	0.096
Vitreous seed features			
Active vitreous seeds	12 (29)	27 (55)	0.012
Quadrants involved			0.342
1 Quadrant	7 (58)	9 (33)	1.000
2 Quadrants	1 (9)	8 (30)	0.026
3 Quadrants	0 (0)	1 (4)	1.000
4 Quadrants	4 (33)	9 (33)	0.368
Anteroposterior location			0.397
Focal (<5 seeds)	0 (0)	1 (4)	1.000
Anterior	0 (0)	2 (7)	0.497
Posterior	9 (25)	13 (48)	0.629
Diffuse (anterior and posterior)	3 (25)	11 (41)	0.078
Subretinal fluid			<0.001
None	9 (21)	14 (29)	0.477
Subtotal < 50% detachment	23 (55)	9 (18)	<0.001
Total retinal detachment	4 (10)	21 (43)	<0.001

(29% vs 55%, $P = 0.012$), and more frequent total retinal detachment (10% vs 43%, $P < 0.001$).

The treatment parameters are listed in Table 3. Regarding IVC, each patient received a mean of 6 planned chemotherapy cycles. In the IAC group, each patient received a mean of 3 planned cycles. Of those who received initial IVC, there were 4 (4/42, 10%) who demonstrated recurrence to warrant secondary IAC for globe salvage.

The treatment outcomes are listed in Table 4. Globe salvage was 67% for IVC and 74% for IAC ($P = 0.499$) (Figs. 1, 2). Subgroup analysis based on the ICRB demonstrated similar globe salvage for groups B (85% vs 100%, $P = 1.000$) and C (100% vs 100%, $P = 1.000$). However, there was significantly higher globe salvage using IAC for group D eyes (48% vs 91%, $P = 0.004$). There was no significant difference for group E (66% vs 48%, $P = 1.000$) due to the limited number of eyes with unilateral group E that received IVC (n = 3). Secondary outcomes revealed significantly better tumor control with IAC for solid tumor (62% vs 92%, $P = 0.002$), subretinal seeds (31% vs 86%, $P = 0.006$), and vitreous seeds (25% vs 74%, $P = 0.006$).

Regarding ocular complications, in the IVC group, there was no ischemic event in the ophthalmic, retinal, or choroidal arterial or venous circulation. In the IAC group, there was ophthalmic artery spasm during or after the procedure with temporary incomplete reduction in flow in 4 patients (8%), central retinal artery reduction in flow in 1 (2%) case, branch retinal artery obstruction in 0 (0%), and partial choroidal ischemia in 1 (2%).

Regarding systemic complications, there were no patients with hearing loss, renal failure, secondary leukemia, or cerebrovascular accident in either group. There were no patients with pinealoblastoma, metastasis, secondary cancers, or death in either group.

DISCUSSION

There is debate in the literature on the risks and benefits of IVC versus IAC for retinoblastoma management. In this analysis, we specifically compared outcomes for only unilateral retinoblastoma. We excluded bilateral cases and previously treated cases to avoid the confounding factors of multiple tumors in each eye, previous exposure to chemotherapy, and possible chemoresistance. Despite our attempt for uniformity in this cohort, there were important differences in the 2 groups (IVC vs IAC) because the eyes managed with IAC demonstrated a greater number of group E eyes (7% vs 43%, $P < 0.001$), larger tumors with greater mean diameter (14 vs 18 mm, $P < 0.001$), and greater thickness (7 vs 10 mm, $P = 0.001$). Furthermore, in the IAC group, there was a greater frequency of tumor-related vitreous seeds (29% vs 55%, $P = 0.012$) and total retinal detachment (10% vs 43%, $P < 0.001$). Even with the more advanced features, overall globe salvage was similar at 67% and 74%, respectively, and there was no significant difference

TABLE 3. Treatment Parameters

Feature	IVC, n (%) (n = 42 eyes)	IAC, n (%) (n = 49 eyes)
IVC parameters		
No. cycles, mean (median, range)	6 (6, 2–6)	NA
Vincristine, etoposide, and carboplatin regimen	42 (100)	NA
IAC features		
No. cycles, mean (median, range)	NA	3 (3, 1–6)
Melphalan 3 mg	NA	5 (10)
Melphalan 5 mg	NA	19 (39)
Melphalan 7.5 mg	NA	4 (8)
Melphalan 5 mg + topotecan 1 mg	NA	12 (24)
Melphalan 7.5 mg + topotecan 1 mg	NA	5 (10)
Melphalan 5 mg + carboplatin 30 mg	NA	3 (7)
Melphalan 7.5 mg + carboplatin 30 mg	NA	1 (2)

For IVC, the chemotherapy dose parameters remained unchanged for all cycles.

For IAC, the chemotherapy dose parameters were adjusted minimally depending on the tumor response, so the total number of chemotherapy combinations may be greater than the number of eyes.

NA indicates not applicable.

in specific globe salvage for group B, C, or E eyes. The lack of significance for group E eyes is likely related to the small cohort treated with IVC. However, IAC performed significantly better in globe salvage for group D eyes (48% vs 91%, $P = 0.004$).

This information regarding IAC superiority in salvaging group D eyes is important because most children with unilateral sporadic retinoblastoma present with group D or E eyes. Unpublished data from our department on 2133 consecutive patients with retinoblastoma managed by our team for the past 4 decades revealed 865 (41%) with unilateral and 1268 (59%) with bilateral disease. Of those with unilateral retinoblastoma, the eyes were classified as group A (n = 37, 4%), group B (n = 126, 15%), group C (n = 50, 6%), group D (n = 229, 26%), group E (n = 421, 49%), and retinocytoma (spontaneously regressed retinoblastoma) (n = 2, <1%). Therefore, groups D and E represent 75% of all unilateral cases in our service. Many of the group D eyes in that database, particularly those evaluated before 1994, were managed with enucleation, but more recently, IVC and IAC have generally been employed. Based on this study, globe salvage for group D eyes can be achieved with IAC in approximately 90% of properly selected cases, and enucleation can possibly be avoided. Most group E eyes have been and continue to be managed with enucleation, particularly because of relatively poor control with chemotherapy (IVC and IAC) and risks for metastatic disease. The combination of IAC and IVC can salvage selected group E eyes.[21]

Previous studies on IAC have included an array of patients, including unilateral and bilateral cases and first-line and second-line therapies.[16,22] First-line IAC has been reported to provide 72% globe control.[16] Second-line IAC has been shown to achieve globe salvage in 62% to 80% of eyes after initial IVC or other therapies.[16,23] Second-line IAC has also been used to *rescue* an eye with recurrence after initial IAC.[24,25] In this current study,

TABLE 4. Treatment Outcomes

Feature	IVC (n = 42 eyes)	IAC (n = 49 eyes)	*P*
Mean (median, range) follow-up, mo	162 (76, 29–251)	43 (20, 14–78)	<0.001
Tumor control [n/total (%)]			
Solid tumor control	26/42 (62)	45/49 (92)	0.002
Subretinal seed control	7/22 (31)	26/30 (86)	0.006
Vitreous seed control	3/12 (25)	20/27 (74)	0.006
Globe salvage [n/total (%)]			
Group A	0/0 (0)	0/0 (0)	1.000
Group B	6/7 (85)	2/2 (100)	1.000
Group C	7/7 (100)	4/4 (100)	1.000
Group D	13/25 (48)	20/22 (91)	0.004
Group E	2/3 (66)	10/21 (48)	1.000
Overall	28/42 (67)	36/49 (74)	0499
Other cancers, n (%)			
Secondary malignancies	0 (0)	0 (0)	1.000
Systemic metastasis	0 (0)	0 (0)	1.000
Pinealoblastoma	0 (0)	0 (0)	1.000
Leukemia	0 (0)	0 (0)	1.000

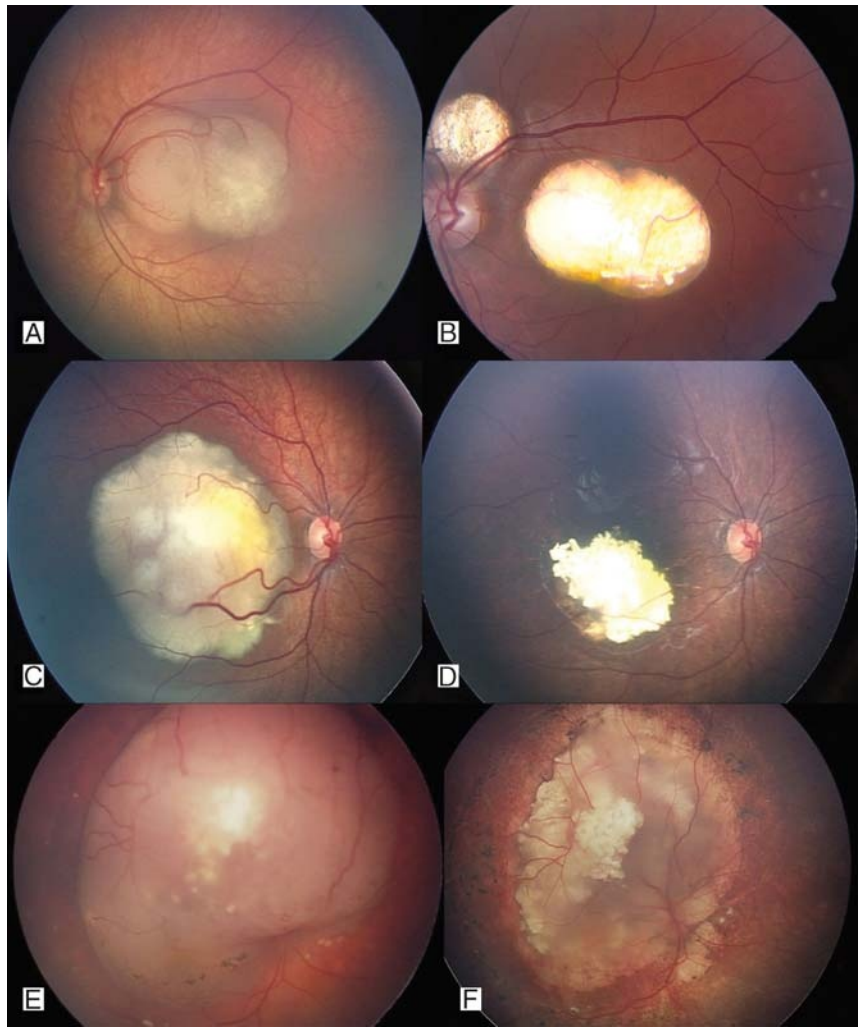

FIGURE 1. Unilateral retinoblastoma managed with IVC. Group B retinoblastoma before (A) and after (B) IVC plus complete macular thermotherapy consolidation. Group C retinoblastoma before (C) and after (D) IVC plus foveal-sparing thermotherapy consolidation. Group D retinoblastoma before (E) and after (F) IVC plus foveal-sparing thermotherapy consolidation.

we specifically studied first-line treatment for unilateral retinoblastoma to better understand the comparative role of IVC versus IAC based on the ICRB.

This is not the first study on chemotherapy for unilateral retinoblastoma. In 2002, IVC for unilateral retinoblastoma was studied using the Reese Ellsworth Classification.[26] By Kaplan-Meier analysis, globe salvage was achieved at 5 years for groups I to IV in 71% and in group V in 33% of cases. Unfortunately, it is not possible to directly compare our results with the Reese Ellsworth Classification because these classifications differ.

To our knowledge, this is the first study to comparatively analyze the outcomes of IVC versus IAC for unilateral retinoblastoma based on the ICRB. Most previous series have explored single-regimen chemotherapy such as IVC alone or IAC alone, often focusing on results of the entire group as a first-line or second-line therapy. Using IVC alone as first-line therapy, globe salvage was found in 100% of group A, 93% of group B, 90% of group C, and 47% of group D, but was not used for group E eyes.[27] In another study using IAC alone as first-line therapy, globe salvage was found in 100% of group B, 100% of group C, 94% of group D, and 36% of group E, but was not used for group A eyes.[16]

In this series, control of solid tumor (62% vs 92%, $P = 0.002$), subretinal seeds (31% vs 86%, $P = 0.006$), and vitreous seeds (25% vs 74%, $P = 0.006$) was significantly better with IAC compared with IVC. Compared with results from single-regimen IVC, 1- and 5-year control of solid tumor was 63% and 49%; subretinal seeds, 47% and 38%; and vitreous seeds, 74% and 50%.[28] Compared with results from single-regimen IAC, 1-year control for solid tumor was 100%; subretinal seeds, 82%; and vitreous seeds, 67%.[15]

Despite the advantages regarding tumor control, IAC carries a higher risk profile for potential vascular compromise to the eye. There have been reports on retinal ischemia, choroidal ischemia, and vision loss after IAC.[22,29–31] In this study, we experienced few vascular events, and most of these occurred in the early years while developing a safe technique for catheterization. Zanaty et al[32] have described these findings and how to technically avoid them. On the other hand, one must consider that IVC usually requires local tumor consolidation with thermotherapy or cryotherapy, which is not routinely necessary with IAC, and this could additionally lead to reduced visual outcome, particularly for macular tumors.

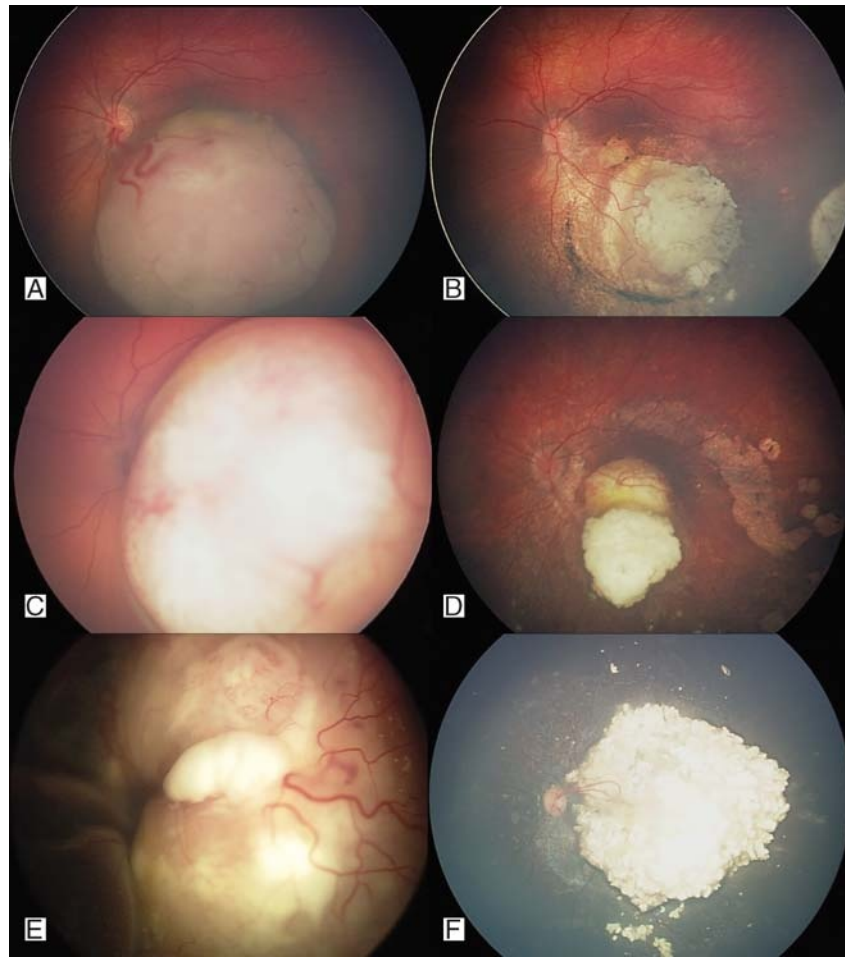

FIGURE 2. Unilateral retinoblastoma managed with IAC alone, without focal consolidation. Group B retinoblastoma before (A) and after (B) IAC. Group C retinoblastoma before (C) and after (D) IAC. Group D retinoblastoma before (E) and after (F) IAC.

There is no universal agreement on the role of IAC versus IVC for retinoblastoma.[18] An opinion report from 4 major centers in Europe, South America, and North America found agreement in preference for IAC for unilateral retinoblastoma. However, there was disagreement for bilateral retinoblastoma because some preferred *tandem* IAC, whereas others favored IVC. Furthermore, IAC is only available at specialized centers. Internationally, particularly in developing nations, the role of IAC remains negligible because of technical and financial concerns.[33] In Africa, for example, the main focus is reliable care to spare the child rather than save the eye. In Chile, IAC has been reduced in cost to an affordable level.[34]

The limitations of this study include its retrospective data collection without randomization. There are many variables that are involved in the strategy of retinoblastoma management. This, combined with the rareness of this disease, makes randomization not feasible. Another limitation was the different baseline tumor features in each group, with greater tumor size and seeding in the IAC group. However, despite worse disease, IAC showed equal or more favorable outcomes. In addition, those patients treated with IVC had longer follow-up than those managed with IAC, and this could have biased the outcomes. However, all patients had a minimum of 1-year follow-up. We believe that our results are representative of the overall perspective and should therefore be considered in the clinician's decision making.

In summary, the current management options for unilateral retinoblastoma include enucleation, IVC, and IAC, along with focal methods depending on tumor size and location. In this retrospective analysis, we specifically compared outcomes of primary IVC versus primary IAC for unilateral retinoblastoma. We found both methods produced similar results for groups B, C, and E, but we noted statistical superiority of IAC for group D retinoblastoma. Based on these findings, IAC should be considered as a reasonable therapeutic alternative for children with unilateral group D retinoblastoma. Future prospective randomized investigations into the conservative management of unilateral retinoblastoma could provide more definitive results regarding tumor control and ocular salvage.

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