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Outcomes of Intravenous Chemotherapy (Chemoreduction) for Retinoblastoma Based on Patient Age in 964 Eyes of 554 Patients.

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Outcomes of Intravenous Chemotherapy (Chemoreduction) for Retinoblastoma Based on Patient Age in 964 Eyes of 554 Patients

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Purpose: To evaluate retinoblastoma control after intravenous chemotherapy (chemoreduction) by patient age at presentation.

Design: Retrospective case series.

Methods: This study included 964 eyes of 554 patients treated with chemoreduction at Ocular Oncology Service at Wills Eye Hospital. Patients received 6 monthly cycles of standard chemoreduction. Additional therapies for tumor control were performed as needed.

Results: Of 964 eyes, a comparison by age group (<6 months vs. 6–12 months vs. 13–24 months vs. >24 months) revealed more advanced age group with higher frequency of group E tumor (15% vs. 25% vs. 32% vs. 39%, $P < 0.001$). By treatment outcomes, complete tumor control was achieved with chemoreduction alone more often in less advanced age group (46% vs. 30% vs. 17% vs. 8%, $P < 0.001$). Additional treatment after chemoreduction was needed more often in more advanced age group with external beam radiotherapy (EBRT; 9% vs. 16% vs. 20% vs. 15%, $P = 0.006$) or enucleation (12% vs. 18% vs. 26% vs. 37%, $P < 0.001$). Over time (1994–1998 vs. 1999–2003 vs. 2004–2008 vs. 2009–2013 vs. 2014–2019), the paradigm for additional required treatment after chemoreduction shifted toward less EBRT (27% vs. 24% vs. 14% vs. 7% vs. 2%, $P < 0.001$) and more intra-arterial (0% vs. 0% vs. 1% vs. 25% vs. 48%, $P < 0.001$) and intravitreal (0% vs. 0% vs. 3% vs. 10% vs. 20%, $P < 0.001$) chemotherapy.

Conclusions: Chemoreduction is a safe and effective treatment method for patients with retinoblastoma, demonstrating the best tumor control in the younger age groups.

Key Words: age, chemoreduction, intravenous chemotherapy, outcomes, retinoblastoma

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The authors have no conflicts of interest to declare.

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Retinoblastoma is the most common primary intraocular malignancy of childhood with approximately 5000 new cases worldwide annually and 250–300 new cases in the United States.[1,2] The management of retinoblastoma is complex and depends on several factors, including patient age, tumor laterality, tumor size and location, and presence of vitreous and subretinal seeds, and retinal detachment and vitreous hemorrhage. Current options for management include intravenous chemotherapy (chemoreduction, CRD), intra-arterial chemotherapy (IAC), intravitreal/intra-aqueous chemotherapy, plaque radiotherapy, and enucleation.[3,4] External beam radiotherapy (EBRT) is no longer used at our institution due to treatment-related complications. Chemoreduction has emerged as an important treatment modality for both unilateral and bilateral retinoblastoma and in all age groups. The terminology "chemoreduction" was introduced to describe the impact of intravenous chemotherapy-induced tumor size reduction and retinal detachment resolution that subsequently allowed for tumor consolidation with transpupillary thermotherapy (TTT) and/or cryotherapy.[5,6]

For over 25 years we have been employing chemoreduction in the management of retinoblastoma, for patients of all ages. We recently explored the 2, 5, 10, and 20-year retinoblastoma control using chemoreduction based on the International Classification of Retinoblastoma (ICRB) group and documented 20-year control for Groups A, B, and C at ≥91%, D at 71%, and E at 32% ($P < 0.001$).[7] Herein, we explore chemoreduction efficacy and safety based on patient age, to specifically understand long-term outcomes of tumor control, treatment-related local and systemic side effects, and life prognosis.

METHODS

Medical records were retrospectively reviewed for patients diagnosed with retinoblastoma and managed with chemoreduction at the Ocular Oncology Service, Wills Eye Hospital, Thomas Jefferson University in conjunction with the Department of Pediatric Oncology, the Children's Hospital of Philadelphia between January 1, 1994 and June 1, 2019. This study was conducted in accordance with the Declaration of Helsinki and approved by the Wills Eye Hospital Institutional Review Board.

Clinical and photographic data were reviewed retrospectively for demographic information, including age at presentation (in months), sex, race (Caucasian, African American, Asian, Hispanic, Central/South Asian, or Middle Eastern), affected eye (right, left, or both), and laterality (unilateral or bilateral). Genetic testing results (somatic, germline with 13q deletion, germline without 13q deletion), hereditary pattern (familial or sporadic), and grouping of retinoblastoma (ICRB Group A, B, C,

D, or E) were also recorded. Classification by ICRB group for patients diagnosed before 2004 was performed retrospectively via fundus drawings and photos. Those who had received chemotherapy elsewhere with an unknown ICRB stage were grouped as "unknown."

A complete ocular examination under general anesthesia was performed by a senior ocular oncologist (C.L.S.). Each retinoblastoma case was evaluated for the total number of tumors per eye, greatest basal dimension and thickness, proximity of the nearest tumor to the optic disc and foveola using indirect ophthalmoscopy and ultrasonography, presence of associated vitreous seeds and number of affected quadrants, presence of subretinal seeds and number of affected quadrants, and presence of subretinal fluid and number of affected quadrants. Anterior segment findings including nystagmus, anterior chamber seeds, and neovascularization of the iris (NVI) were also noted. All findings were documented by fundus drawings, fundus photography (RetCam; Massie Industries), ultrasonography, fluorescein angiography, and optical coherence tomography (OCT; Optovue Incorporated) when available.

All patients were scheduled to receive intravenous chemotherapy. The chemotherapy regimen was recorded, with the predominant regimens including vincristine, etoposide, carboplatin (VEC); vincristine, cisplatin, etoposide, cyclophosphamide, and vincristine, carboplatin. Intravenous chemotherapy with VEC was delivered as follows: carboplatin 18.6 mg/kg for patients $\leq$36 months of age (560 mg/m^2 for patients >36 months of age), etoposide 5 mg/kg daily × 2 days for patients $\leq$36 months of age (150 mg/m^2 daily × 2 days for patients >36 months of age), and vincristine 0.05 mg/kg for patients $\leq$36 months of age (1.5 mg/m^2 for patients >36 months of age). Intensified dosing of VEC was often used for groups D or E disease in the most affected eye: carboplatin 14 mg/kg for patients $\leq$36 months of age daily × 2 days (420 mg/m^2 daily × 2 days for patients >36 months of age), etoposide 6 mg/kg daily × 2 days for patients $\leq$36 months of age (180 mg/m^2 daily × 2 days for patients >36 months of age), and vincristine 0.05 mg/kg for patients $\leq$36 months of age (1.5 mg/m^2 for patients >36 months of age).[8] The intensified regimen was given in conjunction with granulocyte stimulating factor in 1998 and subsequently pegfilgastrim in 2002 (100 μg/kg given once 24 hours after the conclusion of chemotherapy).

At the end of each chemotherapy cycle, ocular oncology follow-up was performed by means of examination under anesthesia. Tumor consolidation in the form of TTT or cryotherapy was performed when necessary. Patients were assessed for new tumor formation and development of tumor recurrence, type of recurrence, interval between the date first seen and development of recurrence (months), and specific treatment for each recurrence. Those with new tumor or recurrence were treated with TTT, cryotherapy, IAC, intravitreal chemotherapy, Iodine-125 plaque radiotherapy, EBRT, or enucleation, depending on new tumor/recurrence size and location.

Patient status at the last follow-up examination was also recorded. The clinical data were analyzed for follow-up period, visual acuity, vitreous hemorrhage, and neovascular glaucoma. Final ocular outcome was success (complete tumor control) or failure (new tumor/recurrence) (need for enucleation/EBRT or need for enucleation/EBRT/IAC/plaque radiotherapy). Pediatric oncology reports were reviewed for hematologic side effects (neutropenia, anemia, thrombocytopenia), vincristine neuropathy, growth delay, and concurrent systemic conditions. Systemic outcomes (metastasis, pinealoblastoma, second cancer, and death) were also noted.

Data were analyzed using the Statistical Package for Social Science (SPSS), version 20 (Armonk, NY: IBM Corp.). Continuous variables are expressed as mean (median, range). The age groups were defined as <6 months, 6–12 months, 13–24 months, and >24 months. These groups were then compared in terms of retinoblastoma treatment success and survival. Normality of the data was tested, and in the presence of a normal distribution, comparisons of variables between age groups were analyzed by ANOVA whereas the Kruskal-Wallis test was used in the absence of a normal distribution. When there was a significant difference, Bonferroni test was used to explore comparisons between groups. Pearson chi-square test was used to analyze categorical variables. A P-value < 0.05 was considered statistically significant.

RESULTS

There were 964 eyes of 554 patients with retinoblastoma included in this series. The patient demographics are listed in Table 1. A comparison by age revealed no difference in sex or affected eye. A comparison by age group (<6 months vs. 6–12 months vs. 13–24 months vs. >24 months) revealed a higher frequency of Caucasian race in the younger age category ($P < 0.001$). With the older age group, there was a lower frequency of bilaterality ($P < 0.001$), higher frequency of group E tumor ($P < 0.001$), lower frequency of germline genetic mutation ($P < 0.001$), and lower frequency of positive family history ($P < 0.001$).

The clinical features are listed in Table 2. A comparison by age group (<6 months vs. 6–12 months vs. 13–24 months vs. >24 months) revealed older age group with fewer total number of tumors per eye ($P < 0.001$), greater tumor basal diameter ($P < 0.001$) and tumor thickness ($P < 0.001$), greater distance to foveola ($P < 0.001$) and optic disc ($P = 0.01$), greater frequency of seeds in the vitreous ($P < 0.001$), subretinal space ($P < 0.001$), and subretinal fluid ($P < 0.001$), more frequent presence of anterior chamber seeds ($P < 0.001$) and iris neovascularization ($P < 0.001$), and less frequent nystagmus ($P = 0.01$).

The treatment features are listed in Table 3. A comparison by age group (<6 months vs. 6–12 months vs. 13–24 months vs. >24 months) revealed older age group with more frequent initial delivery of chemotherapy elsewhere ($P = 0.01$). A comparison by age group revealed no difference in chemotherapy regimen, reason for chemotherapy regimen other than VEC, or frequency of treatment with IAC, intravitreal chemotherapy, or plaque radiotherapy. The older age category revealed fewer number of chemotherapy cycles ($P = 0.001$) and less frequency of treatment with TTT ($P < 0.001$) and cryotherapy ($P < 0.001$). The younger age category revealed more complete tumor control with chemoreduction alone (46% vs. 30% vs. 17% vs. 8%, $P < 0.001$), less need for treatment with EBRT ($P = 0.006$) or enucleation ($P < 0.001$), and less frequency of postenucleation high-risk features ($P < 0.001$).

Outcomes are listed in Table 4. A comparison by age group (<6 months vs. 6–12 months vs. 13–24 months vs. >24 months) revealed older age category with shorter follow-up duration in months ($P < 0.001$), less frequency of patching (16% vs. 19% vs. 11% vs. 6%, $P = 0.01$), less frequency of nystagmus at the date

TABLE 1. Outcomes of Intravenous Chemotherapy (Chemoreduction) for Retinoblastoma Based on Patient Age in 964 Eyes of 554 Patients

	Age					
Patient Demographics	**<6 Months n = 424 Eyes of 248 Patients (%)**	**6–12 Months n = 249 Eyes of 135 Patients (%)**	**13–24 Months n = 190 Eyes of 108 Patients (%)**	**>24 Months n = 101 Eyes of 63 Patients (%)**	***P* Value**	**Total N = 964 Eyes of 554 Patients (%)**
Age at presentation (months) Mean (median, range)	3.1 (4.0, 0.0–6.0)	9.4 (10.2, 7.0–12.0)	17.6 (18.0, 13.0–24.0)	35.6 (32.0, 25.0–84.0)	**<0.001**	10.9 (8.4, 0.0–84.0)
Sex					0.30	
Male	222 (52)	116 (47)	100 (53)	57 (56)		495 (51)
Female	202 (48)	133 (53)	90 (47)	44 (44)		469 (49)
Race					**<0.001**	
Caucasian	295 (70)	159 (64)	103 (54)	65 (64)		622 (64)
African American	33 (8)	36 (15)	21 (11)	9 (9)		99 (10)
Asian	30 (7)	19 (8)	34 (18)	8 (8)		91 (9)
Hispanic	53 (13)	28 (11)	22 (12)	13 (13)		116 (12)
Central/South Asian	10 (2)	2 (1)	4 (2)	2 (2)		18 (2)
Middle Eastern	3 (1)	5 (2)	6 (3)	4 (4)		18 (2)
Affected eye						
OD	215 (51)	130 (52)	95 (50)	53 (53)	0.95	493 (51)
OS	209 (49)	119 (48)	95 (50)	48 (48)		471 (49)
Laterality					**<0.001**	
Unilateral retinoblastoma	43 (10)	36 (14)	36 (19)	27 (27)		142 (15)
Bilateral retinoblastoma	381 (90)	213 (86)	154 (81)	74 (73)		822 (85)
ICRB					**<0.001**	
Group A	32 (8)	12 (5)	7 (4)	3 (3)		54 (6)
Group B	128 (30)	35 (14)	23 (12)	14 (14)		200 (21)
Group C	54 (13)	43 (17)	22 (12)	9 (9)		128 (13)
Group D	84 (20)	79 (32)	52 (27)	19 (19)		234 (24)
Group E	64 (15)	61 (25)	61 (32)	39 (39)		225 (23)
Group Unknown	62 (15)	19 (8)	25 (13)	17 (17)		123 (13)
Genetic testing					**<0.001**	
Somatic mutation	31 (7)	17 (7)	23 (12)	13 (13)		84 (9)
Germline mutation (non del-13q)	243 (57)	128 (51)	73 (38)	38 (38)		482 (50)
Germline mutation (del-13q)	21 (5)	11 (4)	4 (2)	1 (1)		37 (4)
No mutation found	0 (0)	0 (0)	1 (1)	2 (2)		3 (<1)
Not done	129 (30)	93 (37)	89 (47)	47 (47)		358 (37)
Hereditary pattern					**<0.001**	
Familial	132 (31)	25 (10)	13 (7)	4 (4)		174 (18)
Sporadic	292 (69)	224 (90)	177 (93)	97 (96)		790 (82)

ICRB indicates the International Classification of Retinoblastoma.

Group Unknown represents a group of patients initially started on intravenous chemotherapy elsewhere, but then sent to our team for completion of treatment.

Bold values indicate significant *P* values.

last seen (8% vs. 3% vs. 0% vs. 0%, $P < 0.001$), and higher frequency of rhegmatogenous retinal detachment (1% vs. 2% vs. 1% vs. 9%, $P < 0.001$). There was no difference in final visual acuity, patching duration, or time to rhegmatogenous retinal detachment. The older age category demonstrated a greater frequency of side effects of vitreous hemorrhage ($P < 0.001$), neovascular glaucoma (2% vs. 3% vs. 4% vs. 8%, $P = 0.02$), less frequency of new tumor formation ($P < 0.001$), main tumor recurrence ($P < 0.001$), subretinal seed recurrence ($P = 0.02$), and greater frequency of vitreous seed recurrence ($P < 0.001$). Aqueous seed recurrence was rare (0% vs. 0% vs. 1% vs. 3%, $P = 0.23$) and treated with anterior chamber chemotherapy in 1 case, plaque radiotherapy in 2 cases, and EBRT in 1 case. At final follow-up, the younger age category had a greater frequency of complete tumor regression without enucleation ($P < 0.001$). Metastasis (2% vs. 2% vs. 1% vs. 5%, $P = 0.03$) and pinealoblastoma (2% vs. 2% vs. 1% vs. 0%, $P = 0.73$) were rare. Second cancers were rare (0% vs. 3% vs. 4% vs. 2%, $P = 0.25$) and included 4 cases of osteosarcoma, and singular cases of rhabdomyosarcoma, glioblastoma multiforme, leukemia, pituitary tumor, and conjunctival melanoma. Death was rare (1% vs. 2% vs. 0% vs. 3%, $P = 0.29$) and occurred as a result of pinealoblastoma in 4 cases, metastasis in 2 cases, and stroke in 1 case.

Systemic complications are listed in Table 5. A comparison by age group (<6 months vs. 6–12 months vs. 13–24 months vs. >24 months) revealed no difference in hematological side effects, including neutropenia, anemia, or growth abnormality. The younger age category showed a higher frequency of vincristine neuropathy ($P = 0.01$).

Treatment choices by year are listed in Table 6 for additional therapies required after chemoreduction. A comparison by date first seen at Wills Eye Hospital (1994–1998 vs. 1999–2003 vs. 2004–2008 vs. 2009–2013 vs. 2014–2019) revealed that later date first seen had higher frequency of treatment with IAC ($P < 0.001$) and intravitreal chemotherapy ($P < 0.001$) and less frequency of treatment with plaque radiotherapy ($P < 0.001$), external beam radiotherapy ($P < 0.001$), and enucleation ($P = 0.01$).

TABLE 2. Outcomes of Intravenous Chemotherapy (Chemoreduction) for Retinoblastoma Based on Patient Age in 964 Eyes of 554 Patients. Clinical Features at Diagnosis

	Age					
Clinical Features	**<6 Months n = 424 Eyes of 248 Patients (%)**	**6–12 Months n = 249 Eyes of 135 Patients (%)**	**13–24 Months n = 190 Eyes of 108 Patients (%)**	**>24 Months n = 101 Eyes of 63 Patients (%)**	***P* Value**	**Total N = 964 Eyes of 554 Patients (%)**
Number of tumors per eye	2.3	2.2	1.8	1.4	**<0.001**	2.1
Mean (median, range)	(1.0, 1.0–9.0)	(2.0, 1.0–8.0)	(1.0, 1.0–10.0)	(1.0, 1.0–4.0)		(1.0, 1.0–10.0)
Largest diameter (mm)	9	13	12	12	**<0.001**	11
Mean (median, range)	(6, 1–25)	(13, 1–24)	(13, 1–24)	(12, 1–26)		(11, 1–26)
Thickness (mm)	5	7	6	7	**<0.001**	6
Mean (median, range)	(4, 1–23)	(6, 0–16)	(6, 0–20)	(5, 0–19)		(6, 0–23)
Distance to foveola (mm)	1.6	1.9	2.1	3.1	**<0.001**	2.0
Mean (median, range)	(0.0, 0.0–15.0)	(0.0, 0.0–15.0)	(0.0, 0.0–15.0)	(0.0, 0.0–15.0)		(0.0, 0.0–15.0)
Distance to ON (mm)	1.5	1.6	1.7	2.5	**0.01**	1.7
Mean (median, range)	(0.0, 0.0–16.0)	(0.0, 0.0–16.0)	(0.0, 0.0–16.0)	(0.0, 0.0–10.0)		(0.0, 0.0–16.0)
Vitreous seeds					**<0.001**	
None	305 (72)	154 (62)	109 (61)	36 (36)		604 (63)
1 quadrant	34 (8)	27 (11)	22 (12)	9 (9)		92 (10)
2 quadrants	10 (2)	23 (9)	7 (4)	7 (7)		47 (5)
3 quadrants	6 (1)	8 (3)	5 (3)	3 (3)		22 (2)
4 quadrants	15 (4)	25 (10)	24 (13)	27 (27)		91 (10)
No view	54 (13)	12 (5)	23 (13)	19 (19)		108 (11)
Subretinal seeds					**<0.001**	
None	283 (67)	135 (54)	109 (57)	60 (59)		587 (61)
1 quadrant	31 (7)	25 (10)	9 (5)	6 (6)		71 (7)
2 quadrants	34 (8)	37 (15)	17 (9)	1 (1)		89 (9)
3 quadrants	5 (1)	9 (4)	11 (6)	4 (4)		29 (3)
4 quadrants	17 (4)	31 (12)	20 (11)	12 (12)		80 (8)
No view	54 (13)	12 (5)	24 (13)	18 (18)		108 (11)
Subretinal fluid					**<0.001**	
None	237 (56)	111 (45)	97 (51)	53 (53)		498 (52)
≤1 quadrant	44 (10)	25 (10)	10 (5)	5 (5)		84 (9)
2 quadrants	26 (6)	29 (12)	15 (8)	4 (4)		74 (8)
3 quadrants	18 (4)	13 (5)	13 (7)	2 (2)		46 (5)
4 quadrants	44 (10)	59 (24)	33 (17)	19 (19)		155 (16)
No view	55 (13)	12 (5)	22 (12)	18 (18)		107 (11)
Anterior segment findings						
Anterior chamber seeds	1 (<1)	1 (<1)	1 (1)	8 (8)	**<0.001**	11 (1)
Iris neovascularization	10 (2)	17 (7)	12 (6)	19 (19)	**<0.001**	58 (6)
Nystagmus	31 (7)	17 (7)	2 (1)	4 (4)	**0.01**	54 (6)

ON indicates optic nerve.

Bold values indicate significant *P* values.

DISCUSSION

Intravenous chemotherapy (chemoreduction) is an important primary treatment modality for patients with retinoblastoma. This modality was introduced in the mid-1990s and with various combinations of chemotherapeutic agents, but most often employing vincristine, etoposide, and carboplatin. Recently, we reviewed globe salvage with CRD by ICRB group and found tumor control with avoidance of enucleation and/or external beam radiotherapy (Groups A vs. B vs. C vs. D vs. E) at year 2 was (96% vs. 91% vs. 91% vs. 71% vs. 32%, $P < 0.001$) and remained stable up to 20 years.[7] In this current analysis, we specifically focused on treatment success based on patient age at diagnosis and have shown that CRD overall provides control for 80% of cases but with key differences between age groups.

In a recent analysis on 964 eyes treated with CRD, we documented that the more advanced ICRB group (A vs. B vs. C vs. D vs. E) was associated with the older mean age at presentation (8 vs. 7 vs. 10 vs. 11 vs. 15 months).[7] Similarly, in this study, we found that patients with older age at initial presentation (<6 months vs. 6–12 months vs. 13–24 months vs. >24 months) demonstrated a higher frequency of advanced group E retinoblastoma (15% vs. 25% vs. 32% vs. 39%). Regarding tumor laterality, in this series, we found older patients with less frequent germline mutation (57% vs. 51% vs. 38% vs. 38%) or bilateral involvement (90% vs. 86% vs. 81% vs. 73%). Ghassemi et al[9] reviewed 557 cases and found that the mean age at presentation was 24.7 months in germline cases and 35.7 months in nongermline cases. Likewise, prior studies have documented the mean age at diagnosis of bilateral retinoblastoma at approximately 12 months, whereas unilateral disease is diagnosed later at a mean age of 24 months.[1] Thus, older patients could be more likely to present with advanced disease due to diagnostic delay. Consistent with the more advanced ICRB group, we found that older patient age at presentation in our series was associated with greater mean tumor diameter and thickness, higher frequency of vitreous and subretinal seeds, and more subretinal fluid at presentation.

TABLE 3. Outcomes of Intravenous Chemotherapy (Chemoreduction) for Retinoblastoma Based on Patient Age in 869 Eyes of 540 Patients

	Age					
Treatment Features	**<6 months n = 421 Eyes of 245 Patients (%)**	**6–12 Months n = 212 Eyes of 125 Patients (%)**	**13–24 Months n = 149 Eyes of 108 Patients (%)**	**>24 Months n = 87 Eyes of 62 Patients (%)**	***P* Value**	**Total N = 869 Eyes in 540 Patients (%)**
Chemotherapy						N = 869
Chemotherapy at WEH						
Yes	265 (63)	151 (71)	87 (58)	47 (54)	**0.01**	550 (63)
No	156 (37)	61 (29)	62 (42)	40 (46)		319 (37)
Chemotherapy Regimen						
VEC	344 (82)	201 (95)	136 (91)	77 (89)	0.05	758 (87)
Other CT regimens*	77 (18)	11 (5)	13 (9)	10 (12)		111 (13)
Reason for chemotherapy regimen other than VEC	n = 77	n = 11	n = 13	n = 10		n = 111
Hearing loss	7 (9)	0 (0)	0 (0)	0 (0)	0.05	7 (6)
Medication allergy†	9 (12)	6 (55)	4 (31)	0 (0)		19 (17)
Other‡	61 (79)	5 (45)	9 (69)	10 (100)		85 (77)
Number of cycles of chemotherapy mean (median, range)	6 (6, 1–19)	6 (6, 2–15)	6 (6, 1–24)	5 (6, 1–9)	**0.001**	6 (6, 1–24)
Focal therapy						
Transpupillary thermotherapy						
Number of eyes	221 (53)	86 (41)	42 (28)	20 (23)	**<0.001**	369 (42)
Number of sessions Mean (median, range)	2 (1, 0–8)	1 (0, 0–7)	1 (0, 0–7)	1 (0, 0–5)	**<0.001**	1 (0, 0–8)
Cryotherapy						
Number of eyes	226 (54)	123 (58)	60 (40)	31 (36)	**<0.001**	440 (51)
Number of sessions mean (median, range)	2 (1, 0–17)	2 (1, 0–11)	1 (0, 0–11)	1 (0, 0–6)	**<0.001**	2 (0, 0–17)
Recurrence/non-response with need for further therapy						
IAC						
Number of eyes	80 (19)	27 (13)	25 (17)	20 (23)	0.10	152 (17)
Time to IAC mean (median, range)	3 (2, 0–8)	3 (2, 1–6)	4 (2, 1–7)	5 (4, 1–44)	**0.02**	5 (2, 0–44)
Number of sessions mean (median, range)	3 (3, 1–8)	2 (2, 1–8)	3 (3, 1–8)	3 (3, 2–7)	0.16	3 (3, 1–8)
Intravitreal injection	n = 27 (6)	n = 13 (6)	n = 14 (9)	n = 11 (13)		n = 65 (7)
Melphalan	15 (4)	6 (3)	6 (4)	5 (6)	0.47	32 (4)
Topotecan	2 (1)	1 (<1)	1 (1)	0 (0)		4 (1)
Melphalan+Topotecan	10 (3)	6 (3)	7 (5)	5 (6)		28 (3)
Methotrexate	0 (0)	0 (0)	0 (0)	1 (1)		1 (<1)
Number of injections mean (median, range)	4 (3, 1–10)	4 (3, 1–10)	5 (5, 1–8)	4 (5, 2–7)	0.61	4 (3, 1–10)
Plaque radiotherapy						
Number of eyes	92 (22)	38 (18)	25 (17)	14 (16)	0.33	169 (19)
Time to plaque Mean (median, range)	13 (10, 1–62)	11 (9, 1–47)	13 (9, 1–79)	8 (6, 1–17)	0.73	13 (9, 1–79)
EBRT						
Number of eyes	39 (9)	35 (16)	30 (20)	13 (15)	**0.006**	117 (14)
Time to EBRT mean (median, range)	6 (2, 1–38)	7 (6, 2–19)	14 (4, 1–124)	4 (4, 0–11)	0.14	8 (5, 1–124)
Enucleation						
Number of eyes	52 (12)	38 (18)	39 (26)	32 (37)	**<0.001**	161 (19)
Time to enucleation mean (median, range)	18 (10, 1–191)	18 (16, 1–91)	14 (9, 1–60)	9 (8, 1–28)	0.20	15 (11, 1–191)
Reason for enucleation	n = 46	n = 38	n = 38	n = 31		n = 154
Blind painful eye/phthisis	12 (26)	16 (42)	11 (29)	9 (29)	0.24	48 (31)
Active tumor	30 (65)	20 (53)	21 (55)	19 (61)		90 (58)
Optic nerve invasion	0 (0)	2 (5)	3 (8)	0 (0)		5 (3)
Enucleated elsewhere	4 (9)	0 (0)	3 (8)	3 (10)		10 (7)
Histopathological high risk features						
Number of eyes	5 (1)	2 (1)	9 (6)	6 (7)	**<0.001**	22 (2)
Retrolaminar optic nerve invasion	1 (20)	2 (100)	7 (78)	4 (67)	0.29	14 (64)
Anterior segment involvement	0 (0)	0 (0)	1 (11)	1 (17)		2 (9)
Ciliary body involvement	1 (20)	0 (0)	0 (0)	0 (0)		1 (5)
Massive choroidal invasion	3 (60)	0 (0)	1 (11)	1 (17)		5 (23)

C indicates carboplatin; CT, chemotherapy; E, etoposide; EBRT, external beam radiotherapy; IAC, intra-arterial chemotherapy; V, vincristine; WEH, Wills Eye Hospital.

Bold values indicate significant *P* values.

*Others include various combinations of vincristine, carboplatin, etoposide, cyclophosphamide, ifosfamide, topotecan, doxorubicin, methotrexate, and artesunate.

†Medication allergy includes vincristine, carboplatin, and etoposide.

‡Others include: low blood counts, solitary kidney, CHOP study protocol, treatment given elsewhere, and no reason mentioned.

TABLE 4. Outcomes of Intravenous Chemotherapy (Chemoreduction) for Retinoblastoma Based on Patient Age in 869 Eyes of 540 Patients. Outcomes

	Age					
	<6 Months n = 421 Eyes of 245 Patients (%)	**6–12 Months n = 212 Eyes of 125 Patients (%)**	**13–24 Months n = 149 Eyes of 108 Patients (%)**	**>24 Months n = 87 Eyes of 62 Patients (%)**	***P* Value**	**Total N = 869 Eyes in 540 Patients (%)**
Follow-up (months) Mean (median, range)	76 (59, 0–264)	90 (67, 0–299)	75 (57, 0–288)	51 (38, 0–220)	**<0.001**	77 (57, 0–299)
Visual acuity						
Preverbal						
Fix and follow	96 (23)	44 (21)	29 (19)	7 (8)	**0.02**	176 (20)
No fix or follow	3 (1)	3 (14)	0 (0)	2 (2)		8 (1)
Snellen						
≥20/40	80 (19)	43 (20)	30 (20)	23 (26)	0.07	176 (20)
20/50–20/400	77 (18)	44 (21)	27 (17)	6 (7)		154 (18)
<20/400	63 (15)	30 (14)	18 (12)	9 (10)		120 (14)
Enucleation	52 (12)	40 (19)	39 (26)	33 (38)	0.44	164 (19)
Not available	50 (12)	8 (4)	6 (4)	7 (8)		71 (8)
Vitreous hemorrhage	37 (9)	32 (15)	33 (22)	13 (15)	**<0.001**	115 (13)
Time to VH (months) Mean (median, range)	19 (16, 0–62)	36 (16, 0–208)	8 (3, 0–36)	9 (5, 0–29)	**0.002**	19 (10, 0–208)
New tumor formation	90 (21)	22 (10)	2 (1)	4 (5)	**<0.001**	118 (13)
Time to new tumor formation (months) Mean (median, range)	8 (3, 1–187)	4 (3, 1–17)	17 (17, 1–35)	17 (2, 1–64)	0.57	8 (3, 0–187)
Treatment	n = 90	n = 22	n = 2	n = 4		n = 118
CRD	8 (9)	5 (23)	0 (0)	0 (0)	0.46	13 (11)
Focal therapy	74 (83)	15 (68)	1 (50)	3 (75)		93 (79)
IAC	5 (6)	2 (9)	1 (50)	1 (25)		9 (8)
Plaque radiotherapy	2 (2)	0 (0)	0 (0)	0 (0)		2 (2)
Enucleation	1 (1)	0 (0)	0 (0)	0 (0)		1 (1)
Main tumor recurrence	210 (50)	69 (33)	49 (33)	27 (31)	**<0.001**	355 (41)
Time to main tumor recurrence (months) Mean (median, range)	8 (7, 0–79)	10 (7, 0–131)	6 (1, 0–35)	6 (5, 0–33)	0.16	8 (7, 0–131)
Treatment	n = 210	n = 69	n = 49	n = 27		n = 355
CRD	5 (2)	3 (4)	4 (8)	0 (0)	**<0.001**	12 (3)
Focal	86 (41)	24 (35)	8 (16)	3 (11)		121 (34)
IAC	41 (20)	10 (15)	16 (33)	6 (22)		73 (21)
Plaque radiotherapy	59 (28)	19 (28)	11 (22)	8 (30)		97 (27)
EBRT	14 (7)	7 (10)	6 (12)	4 (15)		31 (9)
Enucleation	5 (2)	6 (9)	4 (8)	6 (22)		21 (6)
Vitreous seed recurrence	50 (12)	44 (21)	38 (26)	30 (35)	**<0.001**	162 (19)
Time to vitreous seed recurrence (months) Mean (median, range)	9 (7, 0–33)	12 (8, 0–129)	9 (6, 0–46)	8 (7, 0–28)	0.48	10 (7, 0–129)
Treatment	n = 50	n = 44	n = 38	n = 30		n = 162
CRD	0 (0)	3 (7)	5 (13)	0 (0)	**<0.001**	8 (5)
Focal*	9 (18)	10 (23)	5 (13)	1 (3)		25 (15)
IAC	6 (12)	6 (14)	3 (8)	4 (13)		19 (12)
Intravitreal chemotherapy	18 (36)	6 (14)	9 (24)	8 (27)		41 (25)
Plaque radiotherapy	11 (22)	9 (21)	2 (6)	3 (11)		25 (16)
EBRT	2 (4)	7 (16)	6 (17)	2 (7)		17 (10)
Enucleation	4 (8)	3 (7)	8 (22)	12 (44)		27 (18)
Subretinal seed recurrence	112 (27)	76 (36)	35 (24)	21 (24)	**0.02**	244 (28)
Time to subretinal seed recurrence (months) Mean (median, range)	7 (6, 0–76)	9 (7, 0–129)	13 (6, 0–140)	11 (4, 0–133)	0.40	9 (6, 0–140)
Treatment	n = 112	n = 76	n = 35	n = 21		n = 244
CRD	1 (1)	2 (3)	1 (3)	0 (0)	0.47	4 (2)
Focal*	64 (57)	42 (55)	19 (54)	6 (29)		131 (53)
IAC	23 (21)	17 (22)	11 (31)	8 (38)		59 (24)
Intravitreal chemotherapy	0 (0)	0 (0)	0 (0)	0 (0)		0 (0)
Plaque radiotherapy	7 (6)	4 (5)	0 (0)	1 (5)		12 (5)
EBRT	12 (11)	7 (9)	2 (6)	2 (10)		23 (9)
Enucleation	5 (5)	4 (5)	2 (6)	4 (19)		15 (6)
Tumor status at last follow-up						
Regressed	320 (76)	153 (72)	89 (60)	42 (48)	**<0.001**	604 (70)
Active treatment (improving)	41 (10)	9 (4)	21 (14)	12 (14)		83 (10)
Active treatment (progressing)	2 (1)	3 (1)	0 (0)	0 (0)		5 (1)
Enucleation	52 (12)	40 (19)	39 (26)	33 (38)		164 (19)
Unknown	6 (1)	7 (3)	0 (0)	0 (0)		13 (2)
Pineal cyst	27 (11)	9 (7)	6 (6)	3 (5)	0.52	45 (8)
Time to pineal cyst (months) Mean (median, range)	19 (12, 0–57)	31 (1, 0–176)	15 (2, 0–31)	18 (24, 0–31)	0.76	21 (8, 0–176)

CRD indicates chemoreduction; EBRT, external beam radiotherapy; IAC, intra-arterial chemotherapy; VH, vitreous hemorrhage.

Bold values indicate significant *P* values.

*Including anterior chamber chemotherapy.

TABLE 5. Outcomes of Intravenous Chemotherapy (Chemoreduction) for Retinoblastoma Based on Patient Age in 869 Eyes of 540 Patients. Systemic Complications

	Age					
	<6 Months n = 421 Eyes of 245 Patients (%)	**6–12 Months n = 212 Eyes of 125 Patients (%)**	**13–24 Months n = 149 Eyes of 108 Patients (%)**	**>24 Months n = 87 Eyes of 62 Patients (%)**	***P* Value**	**Total N = 869 Eyes in 540 Patients (%)**
Hematological side effects	160 (38)	91 (43)	44 (30)	33 (38)	0.08	328 (38)
Neutropenia	117 (28)	72 (34)	34 (23)	28 (32)	0.11	251 (29)
Anemia	100 (24)	48 (23)	12 (8)	23 (26)	0.05	183 (21)
Thrombocytopenia	63 (15)	35 (17)	19 (13)	23 (26)	**0.03**	140 (16)
Vincristine neuropathy	17 (4)	4 (2)	0 (0)	0 (0)	**0.01**	21 (2)
Growth abnormality	38 (9)	7 (3)	4 (3)	4 (5)	0.09	53 (6)
Growth retardation	25 (6)	5 (2)	3 (2)	3 (4)	0.06	36 (4)
Obesity	13 (3)	2 (1)	1 (1)	1 (1)	0.11	17 (2)

Bold values indicate significant *P* values.

TABLE 6. Outcomes of Intravenous Chemotherapy (Chemoreduction) for Retinoblastoma Based on Patient Age in 869 Eyes of 540 Patients. Treatment Choices by Date First Seen

	Date First Seen at Wills Eye Hospital						
	1994-1998 n = 168 Eyes of 102 Patients	**1999-2003 n = 140 Eyes of 88 Patients**	**2004-2008 n = 161 Eyes of 105 Patients**	**2009-2013 n = 183 Eyes of 109 Patients**	**2014-2019 n = 217 Eyes of 136 Patients**	***P* Value**	**Total N = 869 Eyes of 540 Patients**
Additional treatment received	n = 126	n = 89	n = 102	n = 146	n = 201		n = 664
Intra-arterial chemotherapy	0 (0)	0 (0)	1 (1)	46 (25)	105 (48)	**<0.001**	152 (17)
Intravitreal chemotherapy	0 (0)	0 (0)	4 (3)	18 (10)	43 (20)	**<0.001**	65 (7)
Plaque radiotherapy	44 (26)	28 (20)	45 (28)	32 (18)	20 (9)	**<0.001**	169 (19)
External beam radiotherapy	45 (27)	33 (24)	23 (14)	12 (7)	4 (2)	**<0.001**	117 (14)
Enucleation	37 (22)	28 (20)	29 (18)	38 (21)	29 (13)	**0.01**	161 (19)

Bold values indicate significant *P* values.

Regarding treatment differences between age groups, we observed that the older patient category (<6 months vs. 6–12 months vs. 13–24 months vs. >24 months) demonstrated more frequent need for adjuvant therapy to achieve globe salvage, including IAC (19% vs. 13% vs. 17% vs. 23%) and intravitreal chemotherapy (6% vs. 6% vs. 9% vs. 13%). Patients at the greatest risk for requiring EBRT or enucleation were also older patients with more advanced ICRB group. Shields et al[10] reviewed 70 patients with retinoblastoma treated with intra-arterial chemotherapy as primary or secondary treatment and found globe salvage rates for group B (100%), group C (100%), group D (94%), and group E (36%). These strikingly favorable results suggest that, depending on tumor group at presentation, the addition of primary or secondary IAC and intravitreal chemotherapy may improve globe salvage, especially for older patients who have lower globe salvage rates with CRD alone.

In 2002, Gombos et al[11] evaluated 36 patients with retinoblastoma and found that patients who were less than 2 months of age at diagnosis were less likely to respond completely to intravenous chemotherapy. In contrast, Shields et al documented in 2002 that patients over 1 year of age at presentation had a higher risk for enucleation after chemoreduction.[12] In this current study, we found that the need for enucleation increased with the age category (12% vs. 18% vs. 26% vs. 37%). In fact, our current data confirmed that the youngest age category demonstrated the best long-term response to CRD with the lowest risk for EBRT or enucleation. We suspect that our results could represent more robust data with 421 eyes of 245 patients <6 months of age compared to a previous report[11] in which 6 eyes of 6 patients <2 months of age were evaluated.

The strengths of this study include a detailed long-term follow-up of a large sample size of nearly 1000 eyes at a single center with leadership by a single surgeon for up to 20 years. Each patient had meticulous large drawings with longitudinal data on tumor control regarding specific solid tumor, subretinal seeds, and vitreous seeds, and complications. We recognize that treatment paradigms shifted over the long study period, and we were able to document a transition from the older era of EBRT to the current era of more frequent IAC and intravitreal chemotherapy as secondary treatments when chemoreduction alone did not provide complete tumor control. The limitations of this study include the retrospective nature of data collection and the fact that some patients were initially diagnosed before referral to Wills Eye Hospital but eventually achieved management in our service. We acknowledge that age at diagnosis can be a confounding variable and delays in diagnosis may have changed the age at presentation in some cases, thus causing differences in ICRB classification, need for enucleation, and possible increased risk for metastasis and death.

In summary, we present a large cohort of patients with retinoblastoma and have studied outcomes by age at presentation. We have shown that patients with retinoblastoma in all age groups can be successfully treated with chemoreduction, and, on the basis of our results, we found that older patients had a higher frequency of group E disease and greater need for IAC and intravitreal chemotherapy, whereas younger patients demonstrated higher CRD success with a lower risk for enucleation. This information can provide a perspective regarding the ultimate need for additional therapy in such cases, including IAC or intravitreal chemotherapy.

REFERENCES

1. Shields JA, Shields CL. Management and prognosis of retinoblastoma. In: Shields JA, ed. Intraocular Tumors: A Text and Atlas. Philadelphia, PA: WB Saunders; 1992:377–392.
2. Shields CL, Shields JA. Diagnosis and management of retinoblastoma. *Cancer Control*. 2004;11:317–327.
3. Abramson DH, Shields CL, Munier FL, Chantada GL. Treatment of retinoblastoma in 2015: agreement and disagreement. *JAMA Ophthalmol*. 2015;133:1341–1347.
4. Shields CL, Meadows AT, Leahey AM, Shields JA. Continuing challenges in the management of retinoblastoma with chemotherapy. *Retina*. 2004;24:849–862.
5. Shields CL, Shields JA. Editorial: chemotherapy for retinoblastoma. *Med Pediatr Oncol*. 2002;38:377–378.
6. Shields CL, Shields JA. Recent developments in the management of retinoblastoma. *J Ped Ophthalmol Strab*. 1999;36:8–18.
7. Shields CL, Baş Z, Tadepalli S, et al. Long-term (20-year) real-world outcomes of intravenous chemotherapy (chemoreduction) for retinoblastoma in 964 eyes of 554 patients at a single center. *Br J Ophthalmol*. 2020;104:1548–1555.
8. Shields CL, Fulco EM, Arias JD, et al. Retinoblastoma frontiers with intravenous, intra-arterial, periocular, and intravitreal chemotherapy. *Eye*. 2013;27:253–264.
9. Ghassemi F, Chams H, Sabour S, et al. Characteristics of germline and non-germline retinoblastomas. *J Ophthalmic Vis Res*. 2014;9:188–194.
10. Shields CL, Manjandavida FP, Lally SE, et al. Intra-arterial chemotherapy for retinoblastoma in 70 eyes. *Ophthalmology*. 2014;121:1453–1460.
11. Gombos D, Kelly A, Coen P. Retinoblastoma treated with primary chemotherapy alone: the significance of tumour size, location, and age. *Br J Ophthalmol*. 2002;86:80–83.
12. Shields CL, Honavar SG, Meadows AT, et al. Chemoreduction plus focal therapy for retinoblastoma: factors predictive of need for treatment with external beam radiotherapy or enucleation. *Am J Ophthalmol*. 2002;133:657–664.