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Original Article

Retinoblastoma in older patients: A retrospective comparative analysis of 100 consecutive patients based on age

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Abstract

Purpose: To describe comparative clinical features, treatment, and outcomes of retinoblastoma in patients initially diagnosed at age 4 or older.
Methods: Retrospective case series.
Results: There were 101 eyes in 100 consecutive patients age ≥4 years diagnosed with retinoblastoma. Mean patient age at diagnosis was 6.6 years (median 5.3, range 4.0–41.0 years). Tumors were predominantly classified (International Classification of Retinoblastoma) as group D (31%) or E (65%). Patients were divided by age into 3 groups: young (4–6 years [65%]), middle (>6–8 years [23%]), and older (>8 years [12%]). Comparing by age group (young vs. middle vs. older), mean tumor basal diameter (19.9 vs. 17.3 vs. 17.0 mm, $p = 0.05$) and mean tumor thickness (11.0 vs. 9.4 vs. 7.0 mm, $p < 0.01$) were greatest in the youngest group. Distance to the optic nerve (1.5 vs. 1.7 vs. 5.0 mm, $p = 0.01$) and foveola (1.9 vs. 1.8 vs. 6.0 mm, $p < 0.01$) were greatest in the oldest age group. Objective findings of leukocoria and strabismus were more common in younger patients, while older patients complained of subjective findings, like decreased vision (19% vs. 30% vs. 60%, $p < 0.01$) and floaters (3% vs. 4% vs. 17%, $p = 0.05$). Primary treatment included enucleation (76%) and other modalities (24%). Globe salvage rate was 13%, with no significant difference by age. Comparison of globe salvage by revealed significant improvement between 1974–2008 (6%) and 2009–2017 (38%, $p < 0.01$).
Conclusion: Retinoblastoma in older patients (>8 years) tends to be smaller and more peripherally located, with more subjective presenting symptoms.

Keywords: Eye, Cancer, Retinoblastoma, Late-onset retinoblastoma, Age older, Teenager, Adult, Globe salvage

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Introduction

Retinoblastoma (RB) is generally detected before 3 years of age.[1] For patients with bilateral RB, mean age at detection is 12 months, and in those with unilateral RB, mean age at detection is 24 months.[2] In an analysis of 528 patients with RB managed at a tertiary referral center from 1989 to 2001, mean patient age was 22 months (median 15 months) at the time of referral.[3] Information from the Surveillance Epidemiology and End Results (SEER) database from 1975 to 2010 with a cohort of 1452 patient revealed mean age at detection of 1 year.[2] Detection of RB at ages older than 4 years is considered unusual.[1]

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In 1919, for the first time, Maghy described bilateral RB in an adult, a 20-year-old woman.[4] Since then, RB in older patients has been described in case reports and small case series.[4–14]. The pathophysiology for late-onset development of RB is speculative. Some postulate that it represents malignant transformation of a benign retinoma (retinocytoma),[5,8,15] and others question whether new mutations can exist [6]. Kaliki et al. speculated that RB1 mutation in persistent embryonic retinal cells could unlock the potential for proliferation and ultimately lead to late-onset RB.[6]

In 1991, Shields et al. reviewed 26 cases of RB diagnosed in patients older than 5 years of age and noted several atypical findings of this malignancy in older patients, including hypopyon, hyphema, uveitis, endophthalmitis, and hemorrhage.[5] In their study, 6 of 26 (23%) patients presented with vitreous hemorrhage or inflammation (endophthalmitis-like) that prevented funduscopic identification of the tumor and delayed diagnosis of RB. Advanced disease was common, necessitating enucleation in 24 of 26 (92%) cases.[5] These findings were corroborated in 2015 by Kaliki et al. in a series of 8 adults with RB presenting after age 20 years.[6] Atypical signs were likewise common, and advanced disease required enucleation in 5 of 8 (62%) cases.[6] As a result of atypical findings and delayed diagnosis, older patients with RB have typically been managed with enucleation.[4–14]

In recent years, the management of RB has evolved dramatically with novel use of intravenous, intra-arterial, and intra-vitreous chemotherapy.[16–19] Thus, the clinical course of older patients with RB warrants reexamination. In this report, we explore the presenting symptoms, clinical features, and outcomes of 100 consecutive patients with late-onset RB, diagnosed at age 4 years (48 months) or older.

Methods

All patients with RB managed on the Ocular Oncology Service, Wills Eye Hospital, Thomas Jefferson University, Philadelphia, PA, USA between January 1, 1974 and March 31, 2017 were retrospectively reviewed. Informed consent was obtained from the patient's parent or legal guardian. Institutional Review Board approval was obtained from Wills Eye Hospital, and this study adhered to the tenets of the Declaration of Helsinki and HIPAA.

All patients with newly diagnosed active RB who were ≥4 years (48 months) old at the time of initial diagnosis were included. Patients with an initial diagnosis of retinoma or retinocytoma (also known as arrested retinoblastoma or spontaneously regressed RB) were excluded. Diagnosis of RB was based on ophthalmic examination under general anesthesia with indirect ophthalmoscopy, Retcam fundus photography (Clarity, Pleasanton, CA), fluorescein angiography, and B-scan ultrasonography. Involved eyes were classified according to International Classification of Retinoblastoma (ICRB) group.

Patient data collected included age at diagnosis, sex, race, laterality, genetic pattern when available (somatic/germline), and best corrected visual acuity. Baseline tumor features included laterality, number of tumors, tumor size (largest basal diameter and thickness, in mm), distance of the main - tumor from the foveola and optic disc (in mm), anterior chamber, vitreous and subretinal seeding, intraocular pressure, iris neovascularization, vitreous hemorrhage, and retinal detachment. Tumor treatment included enucleation, intravenous chemotherapy (IVC), intra-arterial chemotherapy (IAC), intravitreal chemotherapy (IVitC), cryotherapy, photocoagulation, plaque radiotherapy, and external beam radiotherapy (EBRT).

Histopathology features of enucleated eyes included anterior chamber involvement, choroidal invasion (focal if <3 mm in diameter and massive if ≥3 mm in diameter), optic nerve invasion (prelaminar, retrolaminar, or tumor at surgical margin), and extraocular involvement. Mean follow-up and mean event-free follow-up were recorded in years. Primary outcomes were globe salvage and status of patient at last follow-up (alive and well, alive with metastasis, expired due to metastasis, or expired due to unrelated causes).

Data were recorded and tabulated in Microsoft Excel 2011 (Microsoft, Seattle, WA). Analyses for measures of central tendency (mean and median), range, and frequency were performed using built-in functions of the software. Subgroup analysis by age (4–6 years, >6–8 years, and >8 years) was performed to determine differences between groups. JMP statistical analysis software (JMP Pro 13.0.0, Cary, NC) was used to compare categorical and continuous data between groups using Fisher's exact test and ANOVA.

Results

There were 101 eyes in 100 consecutive patients with RB age ≥4 years at initial diagnosis. Patient demographics are listed in Table 1. Mean age at initial diagnosis was 6.6 years (median 5.3, range 4.0–41.0). A comparison of 3 age groups (young [4–6 years] vs. middle [>6–8 years] vs. older [>8 years]) revealed significant differences in female sex (58% vs. 30% vs. 33%, $p = 0.03$). Genetic testing was conducted in 28 (28%) cases, revealing somatic mutation in 22 (22%) and germline mutation in 6 (6%). Presenting symptoms of leukocoria (62% vs. 39% vs. 25%, $p < 0.01$) and strabismus (12% vs. 4% vs. 0%, $p = 0.10$) were more common in the younger age groups, while older patients complained more often of decreased vision (19% vs. 30% vs. 60%, $p < 0.01$) and floaters (3% vs. 4% vs. 17%, $p = 0.05$).

Tumor classification (IRCB) varied between age groups, with a higher prevalence of group E (58% vs. 83% vs. 67%, $p = 0.03$) in the middle and older groups. There was no significant difference in visual acuity ≥20/200 (30%) and <20/200 (70%) by age ($p = 0.21$).

A comparison of tumor features by age (Table 1) revealed that older patients had smaller tumors by mean largest basal diameter (19.9 vs 17.3 vs 17.0 mm, $p = 0.05$) and mean thickness (11.0 vs. 9.4 vs. 7.0 mm, $p < 0.01$). In older patients, tumors were more peripheral, with greater mean distance from the optic nerve (1.5 vs. 1.7 vs. 5.0 mm, $p = 0.01$) and foveola (1.9 vs. 1.8 vs. 6.0 mm, $p < 0.01$). Presence of anterior segment seeds (11% vs. 43% vs. 8%, $p < 0.01$), retinal detachment (62% vs. 48% vs. 33%, $p = 0.05$), and subretinal seeds (83% vs. 65% vs. 58%, $p = 0.02$) varied significantly by age group. There was no significant difference by age in the prevalence of neovascular glaucoma ($p = 0.34$), vitreous seeds ($p = 0.14$), and vitreous hemorrhage ($p = 0.67$).

Treatment features and outcomes are listed in Table 2. Primary treatment included enucleation (76%), IVC (5%), IAC (8%), plaque radiotherapy (5%), and EBRT (6%). Use of EBRT was significantly higher in the older age group (5% vs. 0% vs.

Table 1. Comparative analysis of 100 consecutive patients with active retinoblastoma in 101 eyes at an older age (≥4-years-old). Patient demographics and clinical features.

	Patient age at initial presentation				
	4–6 years old	>6–8 years old	>8 years old	*p*-value	Combined
Patient demographics	(n = 65) [n (%)]	(n = 23) [n (%)]	(n = 12) [n (%)]		(n = 100) [n (%)]
Age at presentation (years)[mean (median, range)]	4.7 (4.6, 4–6)	6.9 (6.6, 6.2–8)	16.4 (11.7, 8.3–40.5)	**<0.01**	6.6 (5.3, 4.0–40.5)
Sex					
Male	27 (42)	16 (70)	8 (67)		51 (51)
Female	38 (58)	7 (30)	4 (33)	**0.03**	49 (49)
Presenting symptom					
Decreased vision	12 (19)	7 (30)	7 (60)	**<0.01**	26 (26)
Leukocoria	40 (62)	9 (39)	3 (25)	**<0.01**	52 (52)
Strabismus	8 (12)	1 (4)	0 (0)	0.10	9 (9)
Hypopyon	0 (0)	1 (4)	0 (0)	0.07	1 (1)
Redness	2 (3)	2 (8)	0 (0)	0.16	4 (4)
Pain	1 (2)	1 (4)	0 (0)	0.33	2 (2)
Floaters	2 (3)	1 (4)	2 (17)	0.05	5 (5)
None	1 (2)	1 (4)	0 (0)	0.33	2 (2)
Genetic testing					
Somatic mutation	16 (25)	4 (18)	2 (17)	0.35	22 (22)
Germline mutation	3 (4)	1 (4)	2 (17)	0.10	6 (6)
Not available	46 (71)	18 (78)	8 (67)	0.41	72 (72)
Affected eye(s)					
Unilateral Rb	63 (97)	22 (96)	11 (92)	0.68	96 (96)
Bilateral Rb	1 (2)	0 (0)	0 (0)	0.46	1 (1)
Contralateral retinoma	1 (2)	1 (4)	1 (9)	0.18	3 (3)
Clinical Features	(n = 66) [n (%)]	(n = 23) [n (%)]	(n = 12) [n (%)]		(n = 100) [n (%)]
ICRB classification					
Group B	1 (1)	1 (4)	0 (0)	0.33	2 (2)
Group C	2 (3)	1 (4)	0 (0)	0.47	3 (3)
Group D	25 (38)	2 (9)	4 (33)	**<0.01**	31 (30)
Group E	38 (58)	19 (83)	8 (67)	**0.03**	65 (65)
Tumors per eye [mean (median, range)]	1 (1; 1–2)	1 (1; 1–2)	1 (1; 1–1)	0.61	1 (1; 1–2)
Largest tumor diameter (mm) [mean (median, range)]	19.9 (21.0; 4.5–25.0)	17.3 (18.5; 5.0–25.0)	17.0 (16.0; 11.0–24.0)	**0.05**	19.0 (20.0; 4.5–25.0)
Tumor thickness (mm) [mean (median, range)]	11.0 (10.8; 2.6–18.0)	9.4 (9.0; 2.0–17.0)	7.0 (6.15; 4.0–13.0)	**<0.01**	10.0 (10.0; 2.0–18.0)
Distance to optic nerve (mm) [mean (median, range)]	1.5 (0.0; 0.0–11.0)	1.7 (0.0; 0.0–10.0)	5.0 (3.5; 0.0–10.0)	**0.01**	2.0 (0.0; 0.0–11.0)
Distance to foveola (mm) [mean (median, range)]	1.9 (0.0; 0.0–11.0)	1.8 (0.0; 0.0–9.5)	6.0 (6.0; 0.0–12.0)	**<0.01**	2.0 (0.0; 0.0–12.0)
Vitreous seeds					
None	6 (9)	4 (17)	0 (0)	0.10	10 (10)
Present	57 (86)	19 (83)	12 (100)	0.14	88 (88)
No view	3 (5)	0 (0)	0 (0)	0.19	3 (2)
Subretinal seeds					
None	11 (17)	8 (35)	5 (42)	**0.02**	24 (24)
1 quadrant	4 (6)	0 (0)	0 (0)	0.14	4 (3)
2 quadrants	8 (12)	0 (0)	1 (8)	0.08	9 (9)
3 quadrants	8 (12)	1 (4)	1 (8)	0.27	10 (10)
4 quadrants	12 (18)	6 (26)	2 (17)	0.40	20 (20)
No view	23 (35)	8 (35)	3 (25)	0.48	34 (34)
Retinal detachment					
None	25 (38)	12 (52)	8 (67)	**0.05**	45 (45)
1 quadrant	5 (7.5)	2 (9)	1 (8)	0.86	8 (8)
2 quadrants	9 (14)	3 (13)	0 (0)	0.17	12 (11)
3 quadrants	5 (7.5)	2 (9)	1 (8)	0.86	8 (8)
4 quadrants	22 (33)	4 (17)	2 (17)	0.08	28 (28)
Vitreous hemorrhage	12 (18)	5 (22)	2 (17)	0.67	19 (19)
Anterior segment findings					
Anterior chamber seeds	7 (11)	10 (43)	1 (8)	**<0.01**	18 (18)
Iris neovascularization	24 (36)	9 (39)	3 (25)	0.39	36 (36)
Neovascular glaucoma	15 (23)	7 (30)	2 (17)	0.34	24 (24)
Visual acuity	*(n = 62)*	*(n = 23)*	*(n = 12)*		*(n = 97)*
≥20/200	16 (26)	8 (35)	5 (42)	0.21	29 (30)
<20/200	46 (74)	15 (65)	7 (58)		68 (70)

25%, $p < 0.01$). Secondary enucleation was required in an additional 11 of 24 eyes ($p = 0.70$) following treatment failure with other methods. Globe salvage was achieved in 13% of cases with no significant difference between age groups ($p = 0.07$). By treatment modality, globe salvage was achieved in 4/6 eyes (66%) with EBRT, 2/5 (40%) with plaque,

Table 2. Comparative analysis of 100 consecutive patients with active retinoblastoma in 101 eyes at an older age (≥4-years-old). Treatment features, treatment outcomes, and enucleation histopathologic features.

	Patient age at initial presentation				
	4–6 years old	>6–8 years old	>8 years old	*p*-value	Combined
Treatment type	(n = 66) [n (%)]	(n = 23) [n (%)]	(n = 12) [n (%)]		(n = 101) [n (%)]
Primary enucleation	54 (82)	17 (74)	6 (50)	0.76	77 (76)
EBRT (n = 6)	3 (5)	0 (0)	3 (25)	**<0.01**	6 (6)
Plaque (n = 5)	2 (2)	3 (13)	0 (0)	0.11	5 (5)
Primary IVC (n = 5)	3 (5)	2 (9)	0 (0)	0.51	5 (5)
Primary IAC (n = 8)	4 (6)	1 (4)	3 (25)	**<0.01**	10 (10)
Secondary enucleation total	6 (9)	3 (13)	2 (17)	0.70	11 (11)
Treatment outcomes	(n = 66) [n (%)]	(n = 23) [n (%)]	(n = 12) [n (%)]		(n = 101) [n (%)]
Follow-up (years) [mean (median, range)]	6 (3, 0–34)	5 (4, 1–22)	2 (1, 0–4)	0.37	5 (3; 0–34)
Globe salvage	6 (9)	3 (13)	8 (38)	0.07	13 (13)
Visual acuities of salvage eye					
≥20/200	4 (67)	2 (67)	2 (50)	0.85	8 (8)
<20/200	2 (33)	1 (33)	2 (20)	0.85	5 (5)
Systemic metastasis*	1 (2)	1 (4)	0 (0)	0.55	2 (2)
Histopathologic features	(n = 57)+ [n (%)]	(n = 20) [n (%)]	(n = 8) [n (%)]		(n = 85) [n (%)]
Optic nerve involvement	22 (39)	5 (25)	2 (25)	0.46	29 (34)
Prelaminar	14 (25)	2 (10)	0 (0)	0.13	16 (19)
Postlaminar	8 (14)	2 (10)	2 (25)	0.59	12 (14)
Tumor cells at surgical sect.	0 (0)	1 (5)	0 (0)	0.19	1 (1)
Choroidal involvement	17 (30)	6 (30)	2 (25)	0.96	25 (29)
Focal (<3mm)	5 (9)	4 (20)	1 (13)	0.41	10 (12)
Massive (≥3mm)	10 (18)	2 (10)	1 (13)	0.70	13 (15)
Not described	2 (3)	0 (0)	0 (0)	0.60	2 (2)
Extraocular extension	1 (2)	1 (5)	0 (0)	0.64	2 (2)
Anterior chamber involvement	3 (5)	9 (45)	3 (38)	**<0.01**	15 (18)

* Both patients with systemic metastasis expired.
\+ Histopathologic features were not available for 3 enucleations in the 4–6 years old group performed elsewhere.

2/5 (40%) with IVC, and 5/8 (63%) with IAC. Globe salvage varied by ICRB groups, including Group B (n = 2/2, 100%), C (n = 1/3, 33%), D (n = 5/31, 16%), and E (n = 5/65, 4%). There was no significant difference in visual acuity ≥ 20/200 (n = 8, 62%) and < 20/200 (n = 5, 38%) by age ($p = 0.21$). Mean follow-up time was 60 months (median 36, range 1–417 months).

Systemic metastasis was found in 2 patients for whom brain involvement was the cause of death. One patient presented with massive brain invasion, having been misdiagnosed elsewhere as Coats disease. The patient expired despite targeted treatment with IVC and craniospinal EBRT. The second patient presented in the pre-IVC era (1991) with Group D retinoblastoma OD and underwent urgent enucleation. Pathology demonstrated massive choroidal invasion. Eight months following enucleation, biopsy of a parietal lobe mass confirmed metastasis.

Histopathologic examination was performed on 85 enucleated globes, 3 of which were enucleated elsewhere (Table 2). Anterior chamber involvement was significantly more common in the older group (5% vs. 45% vs. 38%, $p < 0.01$). There was no difference by age for choroidal invasion ($p = 0.96$), optic nerve involvement ($p = 0.46$), postlaminar invasion ($p = 0.59$), or extraocular extension ($p = 0.64$). By histopathologic examination, tumor was present at the optic nerve resection margin in 1 (1%) case.

Patients were also divided into 3 groups by date of initial examination: 1974–1994, 1995–2008, and 2009–2017 (Table 3), with each era corresponding to the advent of a new treatment modality (pre-chemotherapy era, IVC era, and IAC era). Comparison of globe salvage rate by date of initial examination showed significant improvement in the most recent group (11% vs. 2% vs. 38%, $p < 0.01$) (Fig. 1).

Discussion

The differential diagnosis of an amelanotic tumor arising in the fundus of an older child (≥4 years old) or adult includes a variety of inflammatory, infectious, and neoplastic conditions such as retinal and choroidal inflammatory/infectious disease, choroidal nevus, melanoma, lymphoma, osteoma, hemangioma, retinochoroidal leukemia, retinal astrocytic tumors, benign retinoma/retinocytoma, and RB.[1] The overall mean age-adjusted annual incidence of RB is 11.8 per million for children aged 0–4 years.[20] and 0.6 per million in children aged 5 years and older.[21] Approximately 80% of RB cases are diagnosed by age 4,[9] and, according to a study in the Netherlands, screening for hereditary RB is recommended until 4 years of age.[22] In this study, we specifically examined clinical features and outcomes for older patients with RB, diagnosed at age 4 or later.

The diagnosis of RB is readily made when found in a young child with characteristic findings of leukocoria and a white retinal mass. However, older children often present with atypical symptoms or smaller, more peripheral lesions that can simulate infectious or inflammatory etiology and pose a diagnostic dilemma.[5] The most common presenting features for RB in young patients include leukocoria (56%), strabismus

Table 3. Comparative analysis of 100 consecutive patients with active retinoblastoma in 101 eyes at an older age (≥4-years-old). Treatment outcomes by date first seen.

	Year of initial visit				
	1974–1994	1995–2008	2009–2017	*p*-value	Combined
Features	(n = 37) [n (%)]	(n = 43) [n (%)]	(n = 21) [n (%)]		(n = 101) [n (%)]
Follow-up duration (years) [mean (median, range)]	7 (6; 0–34)	5 (4; 0–17)	2 (1; 0–4)	**<0.01**	5 (3; 0–34)*
Event-free follow-up (years) [mean (median, range)]	7 (6; 0–34)	5 (4; 0–17)	1 (1; 0–4)	**<0.01**	5 (3; 0–34)*
Globe salvage	4 (11)	1 (2)	8 (38)	**<0.01**	13 (13)
Systemic metastasis**	1 (3)	0 (0)	1 (8)	0.40	2 (2)
Secondary cancers	0 (0)	0 (0)	0 (0)	0.99	0 (0)

* Three patients were enucleated elsewhere and were lost to follow-up.
** Both patients with systemic metastasis expired.

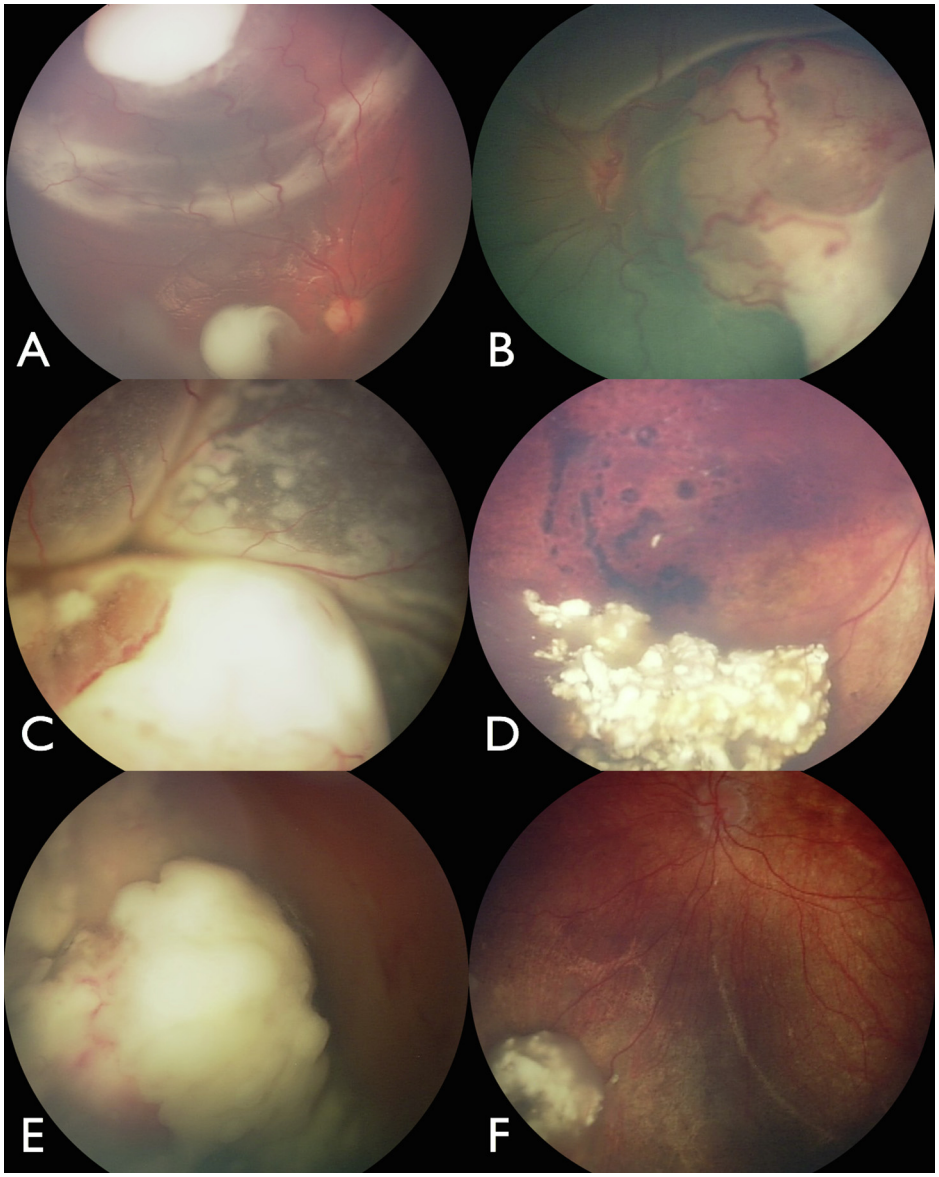

Fig. 1. (A) A 5-year-old boy with group D retinoblastoma (RB) in 2003 was treated with primary enucleation. (B) A 6-year-old boy with group D RB in 2006 was treated with primary enucleation. (C) A 6-year-old girl with group E RB in 2013, was treated with intra-arterial chemotherapy, and showed good tumor regression after 12 months (D). (E) A 6-year-old girl with group D RB in 2016 was treated with intra-arterial chemotherapy and showed good tumor regression after 17 months (F).

(24%), and decreased vision (5%).[23] In a series of older RB patients by Shields et al, subjective symptoms such as decreased vision (35%) were found to be more common than objective findings of leukocoria (35%) and strabismus (15%).[5] In our study, leukocoria (51%), decreased vision (26%), and strabismus (9%) were the most common presenting findings, although we observed a decreased prevalence of leukocoria ($p < 0.01$) and strabismus ($p = 0.1$) with age, consistent with prior reports.[5,13] Moreover, atypical signs of RB, including hypopyon, anterior chamber cells simulating uveitis, and/or vitreous hemorrhage, are known to occur more frequently in cases of late-onset RB and often lead to misdiagnosis with delayed treatment (Fig. 2).[5,12,24] In this study, 14 (14%) patients were initially misdiagnosed, with referring diagnoses of Coats disease (n = 5, 5%), uveitis/endophthalmitis (n = 4, 4%), vitreous hemorrhage with retinal detachment (n = 3, 3%), or toxocariasis (n = 2, 2%). Two patients had previously undergone pars plana vitrectomy with biopsy for diagnostic uncertainty elsewhere, and both required urgent primary enucleation by our team, neither developing metastasis. Consideration of RB with atypical features in older patients might prevent unnecessary procedures that often culminate in enucleation.

Analysis of clinical features of RB in this study showed no significant differences by age (age 4–6 vs. >6–8 vs. > 8 years) for vitreous seeds, subretinal seeds, retinal detachment, vitreous hemorrhage, or optic nerve involvement. However, there were significant differences in features by age in that the oldest patients (>8 years) had smaller tumor thickness (11 vs. 9.4 vs. 7.0 mm, $p < 0.01$) and basal diameter (19.9

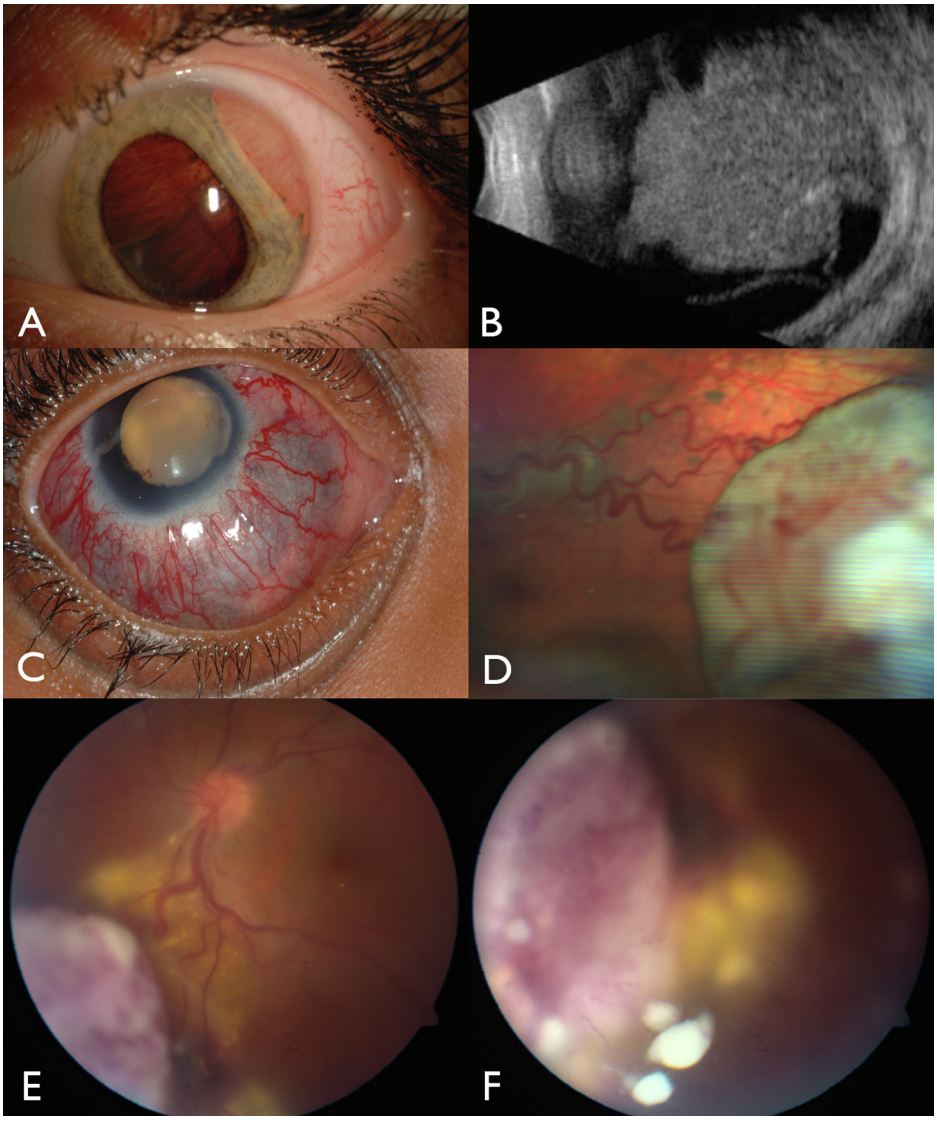

Fig. 2. Atypical features of retinoblastoma (RB) in older patients. (A) A 22-year-old woman with subluxed lens from a (B) mushroom-shaped, minimally calcified ciliochoroidal mass confirmed on cytopathology as RB. (C) A 6-year-old boy, diagnosed elsewhere as Coats disease one year prior, presented with advanced RB with buphthalmos, scleral ectasia, and anterior chamber seeding. (D) An 8-year-old girl with blurry vision was found to have a solitary RB with overlying vitreous seeds. (E) A 23-year-old man noted vision loss and was found to have vitreous hemorrhage from an amelanotic retinal vascular mass with (F) vitreous seeding, suggestive of RB. The patient was successfully treated with intra-arterial and intravitreal chemotherapy.

vs. 17.3 vs. 17.0 mm, $p = 0.05$), with more peripherally located tumors farther from the optic disc (1.5 vs. 1.8 vs. 5.0 mm, $p = 0.01$) and foveola (1.9 vs. 1.8 vs. 6.0 mm, $p < 0.01$). Smaller, more peripheral tumors could be less symptomatic and less easily visualized on funduscopic examination, resulting in delay in diagnosis and treatment in these patients. This is consistent with prior series of adult RB, which reported a mean duration of symptoms before diagnosis of 12–15 months.[6,13] Insidious symptoms in older-onset and adult RB patients can result in loss of considerable time before seeking ophthalmic consultation, which might explain the preponderance for group D (30%) and E (65%) eyes in this study.

Globe-preserving treatment in advanced RB (groups D and E) is challenging and currently involves mostly IAC or IVC.[1] Management of late-onset RB in this series was determined by the stage of disease and standard of care at the time of presentation. Most cases presented with advanced disease requiring enucleation. Primary enucleation was performed for 77 (76%) eyes. Of the remaining 24 (24%) eyes, which were treated with chemotherapy (IVC or IAC) and/or radiation (EBRT or plaque radiotherapy), treatment failure occurred in 11 eyes, necessitating secondary enucleation. Although there was no difference for globe salvage between age groups, comparison by date of first visit (Table 3) showed a marked increase of globe salvage from 6% in the pre-chemotherapy and intravenous chemotherapy years (1974–2008) to 38% in the IAC years (2009–2017), reflecting the important roles that IAC (and additional IVitC) have had in improving globe salvage rates.[18,19] A study of 249 eyes by Shields et al. showed that when IVC was used alone as first-line therapy for RB, globe salvage rate was 100% for group A, 93% for group B, 90% for group C, and 47% for group D.[16] Enucleation, rather than IVC, was typically performed for group E.[16] A more recent study by Shields et al. demonstrated that IAC provided significantly improved globe salvage over IVC in group D eyes (91% vs. 47%, $p = 0.004$), with globe salvage of 36% in group E eyes by IAC.[17] Furthermore, the recent introduction of IVitC has further improved globe salvage for group E eyes from 25% before IVitC to 83% after introduction of IVitC.[18,19]

In spite of advanced local disease in 95% of cases in our study, metastatic RB was found in only 2 cases (2%). Both patients presented to us with systemic metastasis secondary to delayed diagnosis. Despite receiving targeted treatment, both patients expired from brain metastasis. New modalities of treatment and the use of IVC (after 1994) have likely contributed to reduction in risk of metastatic disease. Improved detection of RB will likely lead to further reduction in risk of metastasis.

Strengths of our study included mean follow-up of 60 months, access to clinical photographs for all patients, and a large sample size, which allowed us to detect previously unreported trends in RB tumor size and location in older patients. Admittedly, this study contains the weaknesses inherent to any retrospective, non-randomized study, including lack of standardized treatment plans across all patients. However, this study accurately reflects individualized treatments that are tailored to each patient, with the highest standard of care available at the time of first visit being provided. The standard of care during the study period varied widely, as this study spanned three major eras in RB treatment: pre-chemotherapy, IVC, and IAC.

In summary, the diagnosis of RB should be considered for amelanotic fundus tumors in patients of any age group, even in adults. Although globe salvage rates for RB in older patients have historically been poor, early recognition of this entity and trials of newer treatment modalities, particularly IAC and IVitC, can contribute to improved outcomes.

Declaration of Competing Interest

The authors declared that there is no conflict of interest.

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