RETINOBLASTOMA IN INDIA

Clinical Presentation and Outcome in 1,457 Patients (2,074 Eyes)

SWATHI KALIKI, MD,* ANAMIKA PATEL, MD,* SADIYA IRAM, MD,* GEORGE RAMAPPA, BSc,* ASHIK MOHAMED, PhD, MBBS, MTech,† VIJAY A. R. PALKONDA, MD*

Purpose: To study the clinical presentation, treatment, and outcome of patients with retinoblastoma (RB) in India.

Methods: Retrospective study of 1,457 patients with RB (2,074 eyes).

Results: The mean age at presentation of RB was 29 months (median, 24 months; range, <1–370 months). There were 812 (56%) men and 645 (44%) women with unilateral presentation of RB in 57% (n = 834) and bilateral in 43% (n = 623). Familial RB was present in 4% (n = 55). The most common presenting complaints included leukocoria (n = 1,100; 75%), proptosis (n = 91; 6%), strabismus (n = 77; 5%), and red eye (n = 68; 5%). Most (n = 1,889; 91%) tumors were intraocular in location, and 185 (n = 185; 9%) had extraocular tumor extension at presentation. The most common modalities of primary treatment–included systemic chemotherapy (n = 1,171; 60%) and enucleation (n = 674; 35%). At a mean follow-up period of 44 months (median, 30 months; range, 3–234 months), 92% (n = 1,206) were alive, and 108 (8%) patients died because of RB. Based on Kaplan–Meier analysis, the survival at 1, 3, 5, and 10 years was 94%, 91%, 90%, and 89%, respectively.

Conclusion: The most common presenting signs of RB in Asian Indian population are leukocoria and proptosis. With appropriate treatment, the survival rate is favorable at 92%.

RETINA 0:1–13, 2017

India peaks the predicted incidence of retinoblastoma (RB) in the world with more than 1,400 of 8,000 new cases diagnosed each year.[1] The calculation was based on the assumption of uniform incidence of RB among live-born children at 1 in 16,000 live births and population statistics from 2012 Revision of the World Population Prospects by the United Nations.[1] The projection of burden of RB in India based on the data from hospital-based cancer registries and population-based cancer registries from 5 major cities of India (Delhi, Mumbai, Kolkata, Bangalore, and Chennai) of National Cancer Registry Programme; India revealed that there will be at least 1,000 children affected with RB every year.[2] Though there is a high disease burden of RB in India, there is limited information on the clinical presentation, treatment patterns, and survival from the disease.[3–11]

Numerous studies report the clinical presentation and survival patterns of RB from various countries, but most of them are smaller case series or those including data from histopathology records.[3,4,8,12–26] A study on RB in more than 1,400 American patients between 1960 and 1990 revealed that leukocoria (56%) was the most common presenting sign and with appropriate treatment, survival was achieved in 76% to 85% patients.[27,28] Since then, there have been many advances in the management of RB, and the survival has improved significantly in many countries. A study on RB in 1,576 children in Great Britain showed that the estimated 5-year survival rates for unilateral cases increased from 85% to 97% and for bilateral cases increased from 88% to 100% in 1963–1967 and in 1998–2002, respectively.[29] The patterns of clinical presentation and survival vary between each country with highest mortality recorded in Asia (39%) and

From the *Ocular Oncology Service, The Operation Eyesight Universal Institute for Eye Cancer, L V Prasad Eye Institute, Hyderabad, India; and †Ophthalmic Biophysics, L V Prasad Eye Institute, Hyderabad, India.

Supported by The Operation Eyesight Universal Institute for Eye Cancer (S.K.), The Champalimaud Foundation (S.K.), and Hyderabad Eye Research Foundation (S.K.), Hyderabad, India. The funders had no role in the preparation, review, or approval of the article. Statistical analysis performed by A. Mohamed, Ophthalmic Biophysics, L V Prasad Eye Institute, Hyderabad, India.

None of the authors has any conflicting interests to disclose.

Reprint requests: Swathi Kaliki, MD, The Operation Eyesight Universal Institute for Eye Cancer, L V Prasad Eye Institute, Hyderabad 500034; e-mail: kalikiswathi@yahoo.com

Africa (70%) versus high survival rates in Europe (95%) and Northern America (97%).[30] In this study, we investigate the clinical presentation, treatment patterns, and outcomes of RB in Asian Indian children.

Methods

Institutional review board approval was obtained for the study. This was a retrospective study conducted at The Operation Eyesight Universal Institute for Eye Cancer at L V Prasad Eye Institute, Hyderabad, India. A computerized database search was conducted for the diagnosis "Retinoblastoma" from January 2000 to March 2015. The medical records of all patients with RB were reviewed. The patients with adequate data related to clinical presentation and tumor grouping at first visit were included in the study. Those with a minimum follow-up of 3 months or more were included for outcome analysis of actuarial data. Those with inadequate data documentation related to clinical presentation or tumor grouping at first visit were completely excluded from the study. Those with follow-up of <3 months with unknown outcome were excluded from outcome analysis of actuarial data.

The recorded demographic data included sex, age, and tumor laterality. Details of family history of RB and presenting complaints were recorded. Photographic documentation was performed in all cases. The location of tumor (intraocular with or without extraocular tumor extension) was recorded in all cases. All eyes with intraocular tumor were classified based on International Classification of Intraocular Retinoblastoma (ICIoR)[31] and those with extraocular tumor extension were classified based on International Retinoblastoma Staging System (IRSS).[32]

The details of primary treatment (transpupillary thermotherapy, cryotherapy, systemic chemotherapy, external beam radiotherapy, and enucleation) were recorded. Histopathologic features were recorded in eyes that underwent enucleation. The outcome (metastasis, alive, or dead) was recorded.

Table 1. Demographics of Asian Indian Patients Diagnosed With RB

Feature	All Patients n = 1,457 Patients	Years 2000–2005 n = 407	Years 2006–2010 n = 515	Years 2011–2015 n = 535	*P*
Age at presentation (months), n (%)					
Mean (median, range)	29 (24, <1–370)	30 (24, 1–144)	28 (24, <1–152)	29 (23, <1–370)	0.09
≤1 month	14 (1)	2 (<1)	4 (1)	8 (2)	0.23
>1 month to ≤1 year	420 (29)	119 (29)	148 (29)	153 (29)	0.94
>1–5 years	918 (63)	254 (62)	332 (64)	332 (62)	0.92
>5–10 years	97 (7)	31 (8)	29 (6)	37 (7)	0.51
>10 years	8 (<1)	1 (<1)	2 (<1)	5 (1)	0.31
Age at presentation based on tumor laterality (months), n (%)					
Mean (median, range)					
Unilateral	34 (30, <1–370)	34 (33, 1–144)	34 (33, 1–152)	34 (26, 1–370)	0.07
Bilateral	21 (14, <1–276)	22 (14, 1–108)	21 (16, 1–96)	21 (14, 1–276)	0.76
Age at presentation based on sex (months), n (%)					
Mean (median, range)					
Men	29 (24, <1–319)	29 (24, 2–109)	28 (26, 1–152)	30 (24, 1–319)	0.71
Women	28 (24, <1–370)	30 (24, 1–144)	28 (24, 2–132)	27 (20, 1–370)	0.04
Age at presentation based on tumor location at presentation (months), n (%)					
Mean (median, range)					
Intraocular	27 (23, <1–319)	29 (24, 1–144)	27 (24, 1–152)	28 (24, 1–319)	0.11
Extraocular tumor extension	44 (36, 1–370)	37 (36, 1–98)	38 (36, 2–110)	65 (42, 12–370)	0.052
Sex					
Male	812 (56)	245 (60)	275 (53)	292 (55)	0.52
Female	645 (44)	162 (40)	240 (47)	243 (45)	0.40
Known family history of RB, n (%)					
Yes	55 (4)	15 (4)	18 (3)	22 (4)	0.88
No	1,402 (96)	392 (96)	497 (97)	513 (96)	1.00
Tumor laterality, n (%)					
Unilateral	835 (57)	253 (62)	273 (53)	309 (58)	0.35
Bilateral	622 (43)	154 (38)	242 (47)	226 (42)	0.21

Table 2. Presenting Signs of RB in Asian Indian Patients

Presenting Sign	All Patients n = 1,457 Patients	Years 2000–2005 n = 407	Years 2006–2010 n = 515	Years 2011–2015 n = 535	*P*
Leukocoria, n (%)	1,100 (75)	303 (74)	390 (76)	407 (76)	0.98
Proptosis or enlarged eyeball, n (%)	91 (6)	32 (8)	30 (6)	29 (5)	0.32
Strabismus, n (%)	77 (5)	13 (3)	24 (5)	40 (8)	0.02
Red eye, n (%)	68 (5)	24 (6)	19 (4)	25 (5)	0.32
Decreased vision, n (%)	47 (3)	16 (4)	18 (4)	13 (2)	0.42
Eyelid swelling, n (%)	31 (2)	13 (3)	15 (3)	3 (<1)	0.008
Asymptomatic, n (%)	21 (1)	5 (1)	9 (2)	7 (1)	0.77
Watering, n (%)	17 (1)	0 (0)	8 (2)	9 (1)	0.04
Frequent eye rubbing, n (%)	5 (<1)	1 (<1)	2 (<1)	2 (<1)	0.92

Statistical Analysis

All data were analyzed by grouping the patients into three groups (2000–2005, 2006–2010, 2011–2015) based on the year of presentation (Tables 1–3). The data were also analyzed based on geographic distribution (North, East, South, and West India; Table 4) and disease laterality (Unilateral vs. bilateral; Table 5). Kaplan–Meier survival analysis was performed to estimate the probability of survival at 1, 3, 5, and 10 years (Table 6). The statistical packages used for analysis included Origin version 7.0 (OriginLab Corp, Northampton, MA) and STATA version 11.0 (College Station, TX). The descriptive statistics comprised mean, median, range, proportion, cumulative frequency plots of age at diagnosis, and Kaplan–Meier

Table 3. Clinical Features, Treatment, and Outcome of RB in Asian Indian Patients

Feature	All Patients n = 2,074 Eyes	Years 2000–2005 n = 556 Eyes	Years 2006–2010 n = 757 Eyes	Years 2011–2015 n = 761 Eyes	*P*
Tumor location (n = 2,074), n (%)					
Intraocular	1,889 (91)	491 (88)	687 (91)	711 (93)	0.78
Orbital tumor extension	185 (9)	65 (12)	70 (9)	50 (7)	0.01
ICIoR (n = 1,889), n (%)					
Group A	107 (6)	37 (7)	31 (4)	39 (5)	0.11
Group B	278 (15)	63 (11)	111 (15)	104 (14)	0.39
Group C	127 (7)	20 (4)	57 (8)	50 (7)	0.03
Group D	414 (22)	112 (20)	175 (23)	127 (17)	0.02
Group E	963 (51)	259 (47)	313 (41)	391 (51)	0.11
Tumor filling more than 2/3 of the eye	544 (26)	172 (31)	136 (18)	236 (31)	
One or more complications present including secondary glaucoma, anterior chamber seeding, hyphema, opaque media because of vitreous hemorrhage, or orbital cellulitis	419 (20)	87 (16)	177 (23)	155 (20)	
IRSS (n = 2,074), n (%)					
Stage 0	933 (45)	203 (37)	357 (47)	373 (49)	0.01
Stage I	925 (45)	276 (50)	321 (42)	328 (43)	0.23
Stage II	31 (2)	12 (2)	9 (1)	10 (1)	0.33
Stage III	131 (6)	51 (9)	52 (7)	28 (4)	0.001
Stage IV	54 (3)	14 (3)	18 (2)	22 (3)	0.82
Primary treatment (n = 1,952 eyes), n (%)					
Transpupillary thermotherapy	59 (3)	13 (3)	12 (2)	34 (5)	0.004
Cryotherapy	48 (3)	24 (5)	10 (1)	14 (2)	<0.001
Systemic chemotherapy	1,171 (60)	202 (41)	516 (70)	453 (62)	<0.001
Enucleation	674 (35)	245 (50)	200 (27)	229 (31)	<0.001
Denial of treatment, n (%)	122 (6)	69 (14)	19 (3)	34 (5)	<0.001
Death because of metastasis, n (%)	108 (7)	24 (6)	47 (9)	37 (7)	0.31

Table 4. Analysis of Presentation and Survival of Patients With RB Based on Geographic Distribution

Variable	South India n = 875 Patients (1,210 Eyes)	West India n = 246 Patients (367 Eyes)	North India n = 156 Patients (226 Eyes)	East India n = 160 Patients (239 Eyes)	*P*
Age at presentation (months), n (%)					
Mean (median, range)	30 (24, 0.5–370)	26 (22, 0.5–152)	31 (25, 1–276)	26 (24, 0.8–319)	0.09
Sex, n (%)					
Male	467 (53)	137 (56)	88 (56)	108 (68)	0.40
Female	408 (47)	109 (44)	68 (44)	52 (32)	0.21
Most common presenting complaint, n (%)					
Leukocoria	644 (74)	186 (76)	117 (75)	131 (82)	0.88
Tumor laterality, n (%)					
Unilateral	537 (61)	125 (51)	85 (55)	80 (50)	0.27
Bilateral	338 (39)	121 (49)	71 (45)	80 (50)	0.13
Tumor location, n (%)					
Intraocular	1,099 (91)	338 (92)	206 (91)	214 (90)	1.00
Extraocular tumor extension	111 (9)	29 (8)	20 (9)	25 (10)	0.80
ICIoR, n (%)					
Group A	63 (5)	30 (8)	7 (3)	5 (2)	0.007
Group B	143 (12)	53 (14)	36 (16)	41 (17)	0.15
Group C	60 (5)	24 (7)	23 (10)	13 (5)	0.04
Group D	246 (20)	82 (22)	39 (17)	44 (18)	0.61
Group E	587 (49)	149 (41)	101 (45)	111 (46)	0.43
IRSS, n (%)					
Stage 0	508 (42)	184 (50)	112 (50)	109 (46)	0.28
Stage I	573 (47)	148 (40)	88 (39)	104 (44)	0.30
Stage II	18 (2)	6 (2)	6 (3)	1 (<1)	0.28
Stage III	78 (6)	22 (6)	12 (5)	19 (8)	0.73
Stage IV	33 (3)	7 (2)	8 (4)	6 (3)	0.69
Death, n (%)	58 (7)	20 (8)	15 (10)	15 (9)	0.48

The total number of patients is 1,437. Twenty patients were excluded from this analysis because of inadequate data on geographic location.

estimates of probability of survival. The continuous data were checked for normality using Shapiro–Wilk test. The continuous data among the three time periods or the four geographic regions were compared by analysis of variance or Kruskal–Wallis test, the categorical data by chi-square test, and the survival probabilities by Cox Proportional Hazards Model. A *P* value of less than or equal to 0.05 was considered statistically significant. Post hoc analyses by multiple comparisons included chi-square test, Fisher's exact test, and Mann–Whitney *U* test, and Bonferroni corrections were applied. The continuous data between the two laterality datasets were compared by Mann–Whitney test and the categorical data by chi-square test.

Results

Of 1,592 patients diagnosed with RB during the study period, 1,457 patients (2,074 eyes) were included in the study. A total of 135 patients were excluded from the study because of inadequate data. The demographic data are listed in Table 1. The mean age at presentation of RB was 29 months with 93% cases younger than 5 years of age at presentation. Bilateral cases presented at an earlier age compared with unilateral cases (21 months vs. 34 months) (Figure 1A). The age at presentation was comparable in men (29 months) and women (28 months) with no gender bias (Figure 1B). In the cases with a known family history of RB, the mean age at presentation was 24 months (median, 14 months; range, <1–96 months). The mean age at presentation for female children gradually decreased (30 months in Years 2000–2005; 28 months in Years 2006–2010; and 27 months in Years 2011–2015; $P = 0.04$) based on the year of presentation (Figure 1C). The relation between age at presentation and ICIoR and IRSS are depicted in Figure 1, D and E, respectively.

The presenting complaints are listed in Table 2. The three most common presenting complaints were leukocoria (75%), proptosis (6%), and strabismus (5%).

Table 5. Analysis of Presentation and Survival of Patients With RB Based on Disease Laterality

Variable	Unilateral n = 835	Bilateral n = 622	*P*
Age at presentation (months), n (%)			
Mean (median, range)	34 (30, 0.5–370)	21 (14, 0.5–276)	<0.0001
Sex, n (%)			
Male	456 (55)	356 (57)	0.35
Female	379 (45)	266 (43)	
Family history of RB, n (%)			
Yes	11 (1)	44 (7)	<0.0001
No	824 (99)	578 (93)	
Most common presenting complaint, n (%)			
Leukocoria	620 (74)	478 (77)	0.28
Tumor location, n (%)		(n = 1,239)*	
Intraocular	716 (86)	1,167 (94)	<0.0001
Extraocular tumor extension	119 (14)	72 (6)	
ICIoR, n (%)			
Group A	1 (<1)	106 (9)	<0.0001
Group B	17 (2)	261 (21)	<0.0001
Group C	29 (4)	100 (8)	<0.0001
Group D	177 (21)	237 (19)	0.27
Group E	492 (59)	463 (37)	<0.0001
IRSS, n (%)			
Stage 0	120 (14)	816 (66)	<0.0001
Stage I	562 (67)	344 (28)	<0.0001
Stage II	33 (4)	7 (<1)	<0.0001
Stage III	83 (10)	56 (5)	<0.0001
Stage IV	37 (4)	16 (1)	<0.0001
Primary treatment, n (%)	(n = 774)	(n = 1,178)	
Transpupillary thermotherapy	0 (0)	59 (5)	<0.0001
Cryotherapy	2 (<1)	46 (4)	<0.0001
Systemic chemotherapy	244 (32)	927 (79)	<0.0001
Enucleation	528 (68)	146 (12)	<0.0001
Denial of treatment, n (%)	61 (8)	61 (5)	0.03
Death, n (%)	60 (7)	48 (8)	0.78

*Details of 3 eyes were inadequate, and thus, n = 1,239 eyes in 622 patients.

The presentation with the complaints of strabismus and watering increased with the year of presentation (3% and 0% in Years 2000–2005; 5% and 2% in Years 2006–2010; and 8% and 1% in Years 2011–2015; $P = 0.02$ and $P = 0.04$, respectively). The presentation with eyelid swelling decreased with the year of presentation (3% in Years 2000–2005; 3% in Years 2006–2010; and <1% in Years 2011–2015; $P = 0.008$). The classification and staging of RB and primary treatment details are elaborated in Table 3. Most (91%) tumors were intraocular in location with 9% patients presenting with orbital extension of tumor. Over the

Table 6. Kaplan–Meier Analysis of Survival in Asian Indian Patients With RB

	All Patients; % (95% Confidence Interval) n = 1,457	Years 2000–2005; % (95% Confidence Interval) n = 407	Years 2006–2010; % (95% Confidence Interval) n = 515	Years 2011–2015; % (95% Confidence Interval) n = 535	*P*; % (95% Confidence Interval)
Survival at					
1 year	94% (93–96%)	96% (94–98%)	93% (91–96%)	94% (91–96%)	0.15*
3 years	91% (89–92%)	92% (89–95%)	90% (88–93%)	89% (85–93%)	
5 years	90% (87–91%)	91% (88–95%)	89% (86–92%)	89% (85–93%)	
10 years	89% (87–91%)	91% (87–94%)	89% (86–92%)	89% (85–93%)	

*Cox proportional hazards model.

years, the occurrence of extraocular extension of RB decreased (12% in Years 2000–2005; 9% in Years 2006–2010; and 7% in Years 2011–2015; $P = 0.01$). Based on ICIoR classification, 51% of eyes belonged to Group E. Based on IRSS, Stage 0 (45%) was most common. Over the years, the occurrence of ICIoR Group C and IRSS Stage 0 increased (4% and 37% in Years 2000–2005; 8% and 47% in Years 2006–2010; and 7% and 49% in Years 2011–2015; $P = 0.03$ and $P = 0.01$, respectively); and the occurrence of ICIoR Group D and IRSS Stage III decreased (20% and 9% in Years 2000–2005; 23% and 7% in Years 2006–2010; and 17% and 4% in Years 2011–2015; $P = 0.02$ and $P = 0.001$, respectively). The most common modality of treatment was systemic chemotherapy (60%) followed by enucleation (35%). Over the years, the use of systemic chemotherapy increased and the rate of primary enucleation decreased (41% and 50% in Years 2000–2005; 70% and 27% in Years 2006–2010; and 62% and 31% in Years 2011–2015; $P < 0.001$ and $P < 0.001$, respectively). The rate of denial to treatment also decreased with time (14% in Years 2000–2005; 3% in Years 2006–2010; and 5% in Years 2011–2015; $P < 0.001$). Data analysis based on geographic distribution (Table 4) showed no significant difference in the presentation and outcome of the disease.

The data analysis based on disease laterality (Table 5) revealed that there were significant differences between unilateral and bilateral cases. Compared

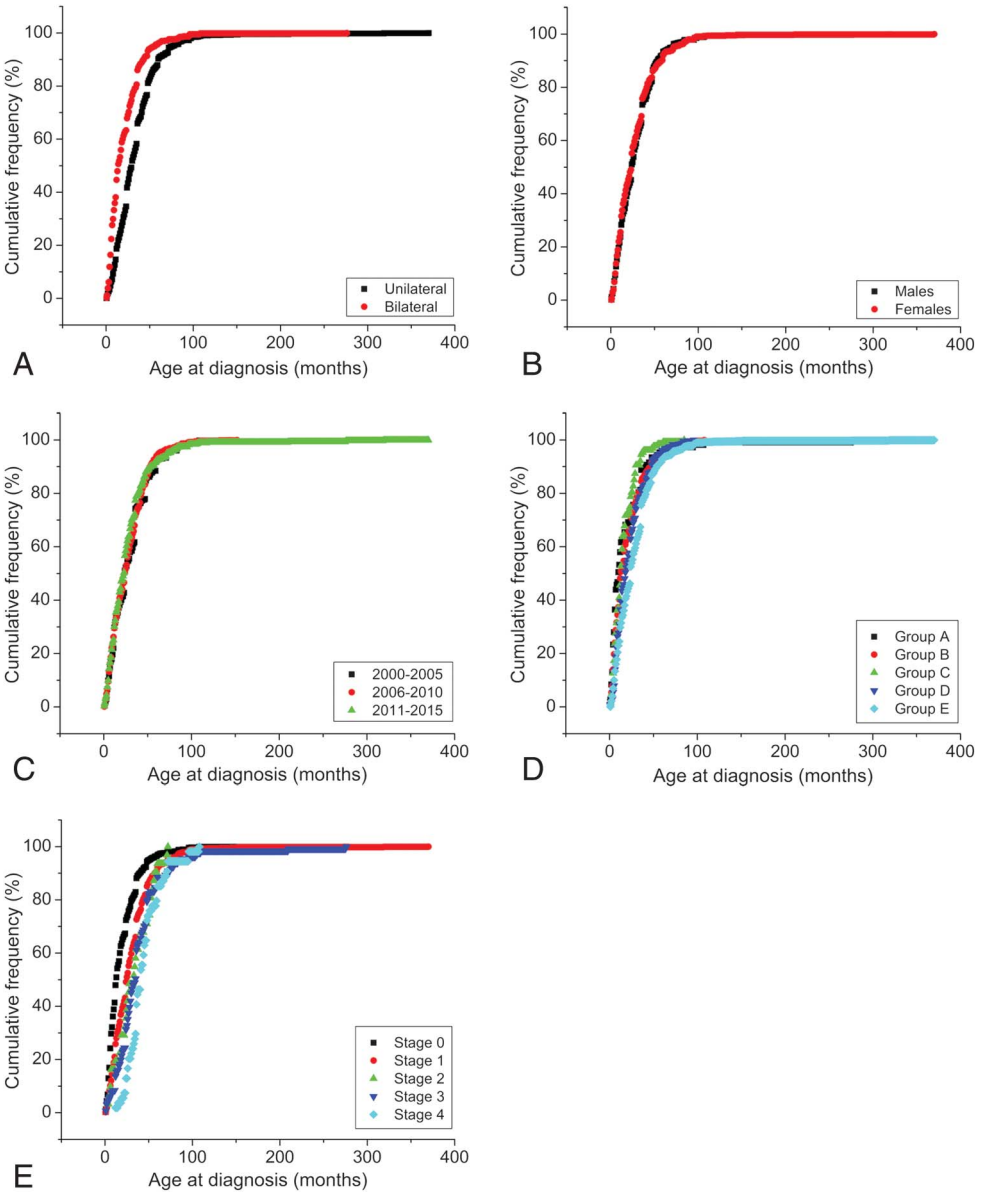

Fig. 1. Cumulative frequency plots of age at diagnosis based on (**A**) disease laterality (**B**) sex (**C**) time period of presentation (**D**) ICIoR (**E**) international staging of RB.

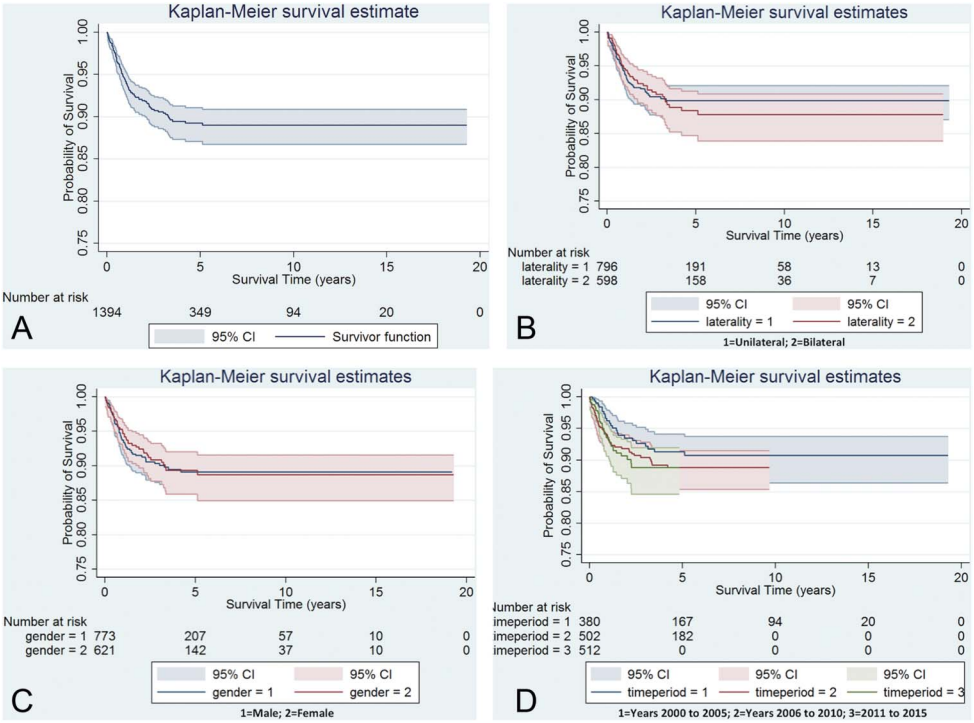

Fig. 2. Kaplan–Meier survival analysis. **A.** Including all cases. **B.** Based on disease laterality. **C.** Based on sex. **D.** Based on time period of presentation.

with unilateral cases, those with bilateral disease were younger at presentation (34 months vs. 21 months; $P < 0.0001$), had a higher rate of positive family history of RB (1% vs. 7%; $P < 0.0001$), were mostly intraocular (86% vs. 94%; $P < 0.0001$), and presented earlier with lower tumor grouping (ICIoR Group A, <1% vs. 9%; $P < 0.0001$, Group B, 2% vs. 21%; $P < 0.0001$, Group C, 4% vs. 8%; $P < 0.0001$, and Group E, 59% vs. 37%; $P < 0.0001$) and staging (IRSS Stage 0, 14% vs. 66%; $P < 0.0001$, Stage I, 67% vs. 28%; $P < 0.0001$, Stage II, 4% vs. <1%; $P < 0.0001$, Stage III, 10% vs. 5%; $P < 0.0001$, and Stage IV, 4% vs. 1%; $P < 0.0001$), and fewer cases underwent primary enucleation (68% vs. 12%; $P < 0.0001$) compared to unilateral cases.

Based on actuarial data (n = 1,314 patients with at least 3-month follow-up and known outcome [alive/dead]), at a mean follow-up period of 44 months (median, 30 months; range, 3–234 months), 92% (n = 1,206) were alive and 108 (8%) patients died because of RB. Based on Kaplan–Meier analysis (Table 6, Figure 2, A–D), the survival at 1, 3, 5, and 10 years was 94%, 91%, 90%, and 89%, respectively. The details of patients who died because of RB are elaborated in Table 7. Based on ICIoR classification, 82% of eyes belonged to Group E. Based on IRSS, Stage IV (44%) was most common. Nineteen (18%) patients were >5 years of age at presentation. Of these, 8 (42%) patients had intraocular disease and 9

Table 7. Details of Patients Who Died Because of RB

Feature (n = 108)	No. (%), n = 108
Age at presentation (months)	
Mean (median; range)	44 (38, 2–276)
Sex	
Male	61 (56)
Female	47 (44)
Tumor laterality and tumor location	
Unilateral	61 (56)
Intraocular	13 (12)
Extraocular tumor extension	48 (44)
Bilateral	47 (44)
Intraocular in both eyes	20 (19)
Extraocular tumor extension in both eyes	2 (2)
Intraocular in one eye and extraocular tumor extension in the other eye	25 (23)
Worse eye: ICIoR (n = 33)	
Group A	0 (0)
Group B	0 (0)
Group C	0 (0)
Group D	6 (18)
Group E	26 (82)
Worse eye: IRSS (n = 108)	
Stage 0	11 (10)
Stage I	16 (15)
Stage II	6 (6)
Stage III	28 (26)
Stage IV	47 (44)

(58%) had extraocular tumor extension on presentation. Of the eight patients with intraocular disease, four underwent primary enucleation, and all of them had high-risk features on histopathology.

Discussion

Retinoblastoma is the most frequent intraocular cancer with more than 8,000 new cases detected each year worldwide, with more than 40% cases detected in Asia-Pacific nations.[1,28] Various studies from different countries have shown that the most common presenting complaints of RB are leukocoria (30–98%) and strabismus (6–24%).[3,12–27] However, in certain regions of Africa and Asia with advanced disease at presentation, the most common presenting complaints are fungating mass (29–46%)[17,32] or proptosis (55–85%).[17,19,20,34] Based on published literature, the presenting complaints are summarized in Table 8.[3,8,12–20,22–27,29,33, 35–76] In our study, the most common presenting complaints were leukocoria (75%), proptosis (6%), and strabismus (5%). Over the years, strabismus as a presenting complaint of RB has increased (P = 0.02) indicating increased awareness of RB presenting as strabismus, and the presentation with eyelid swelling secondary to pseudoorbital cellulitis has decreased (P = 0.008) indicating early diagnosis.

Based on a large data from the United States of America, RB is unilateral in 59% cases and bilateral in 41% cases.[27] Similarly in our series, the tumor was unilateral in 57% cases and bilateral in 43% cases. It is estimated that the mean age at presentation of RB is 18 months, with unilateral cases presenting at a mean age of 24 months and bilateral presenting at 12 months.[77] Compared with the western literature, in our series, there was a delay in the mean age at presentation at 29 months, with bilateral cases presenting at a mean age of 21 months and unilateral cases at 34 months. Our results are comparable to another study of 600 Asian Indian children with RB, where the median age at presentation was 29 months, with unilateral cases presenting at 36 months and bilateral at 18 months.[3] These data suggest that there is delayed referral and poor awareness about the disease in India compared with developed countries. Even in the cases with a known family history of RB, the mean age at presentation was 24 months, indicating the lack of awareness about the hereditary pattern of RB among parents.

In the developed nations, the tumor is mostly intraocular, and extraocular tumor extension on presentation is extremely rare. Extraocular extension of RB is more commonly seen in children from Africa and Asia.[3,5,8–26,33,34] It is mainly attributed to delayed diagnosis and presentation.[78] The occurrence of extraocular tumor extension presenting as proptosis or fungating mass is highest at 65% to 85% in the African countries.[19,20] In our series, 91% tumors were intraocular while 9% had extraocular tumor extension. Among the eyes with intraocular RB, 73% eyes harbored advanced intraocular disease (Group D or E). However, the occurrence of ICIoR Group C has increased (P = 0.03), and the occurrence of ICIoR Group D has decreased (P = 0.02) over the years, indicating a trend toward earlier diagnosis. Of those with orbital tumor extension, 3% already had metastasis at presentation. The mean age at presentation of patients with extraocular tumor extension was higher than those who presented with intraocular disease (44 months vs. 27 months), suggestive of delayed referral and diagnosis. However, over the years, the occurrence of extraocular extension of RB has significantly decreased (P = 0.001), indicating a trend toward earlier diagnosis. In another study of 600 Asian Indian patients, the occurrence of extraocular tumor extension at presentation was much higher compared with our series at 28%.[3] This difference could be related to referral bias and larger cohort of patients in our study.

The management of RB depends on tumor laterality, tumor size, tumor location, visual potential, systemic condition of the patient, and family desires. The various treatment modalities include transpupillary thermotherapy, argon laser photocoagulation, and cryotherapy for smaller tumors or subretinal seeds, systemic chemotherapy, intraarterial chemotherapy, and plaque radiotherapy for solid tumors, intravitreal chemotherapy, periocular chemotherapy, or external beam radiotherapy for vitreous seeds, enucleation for advanced intraocular disease, and multimodal treatment for orbital extension of RB.[79–82] In our series, the most common primary treatment modality was systemic chemotherapy (60%) followed by enucleation (35%). However, at the date last seen, globe salvage was achieved in 45% eyes only, indicating additional 10% eyes undergoing secondary enucleation. However, the rate of globe salvage with conservative treatment (IRSS Stage 0) has improved over the years (P = 0.01). The rate of denial of treatment has also decreased ($P < 0.0001$) over the years, indicating the increasing awareness about the implications and seriousness of the disease. In all cases with orbital extension of RB, a standard protocol of multimodality treatment with chemotherapy (12 doses of high-dose chemotherapy and 6–9 cycles for chemoreduction followed by 3–6 cycles as adjuvant chemotherapy after surgery), surgery (enucleation or orbital exenteration),

Table 8. Comparison of Clinical Presentation and Treatment Outcome of RB Based on Published Literature

Authors	Year of Publication	Study Place	No. of Patients	Most Common Presenting Complaint	Patient Survival Rate	Follow-up Period
Günalp et al[35]	1996	Turkey	636	Leukocoria (62%)	82%	5 years
Abramson et al[27]	1998	USA	1,265	Leukocoria (56%)	—	—
Saw et al[36]	2000	Singapore	46	—	83%	3 years
Sant et al[37]	2001	Europe	954	—	93%	5 years
Kao et al[13]	2002	Taiwan	96	Leukocoria (78%)	64%	1–257 months
Kaimbo et al[16]	2002	Congo	29	Leukocoria (49%)	10%	12–38 months
Leal-Leal et al[38]	2004	Mexico	500	—	89%	73 months
Badhu et al[26]	2005	Eastern Nepal	43	Proptosis (40%)	55%	<1–2 years
Shanmugam et al[8]	2005	India	355	Leukocoria (72%)	99%	Mean, 3 years; range, 0.1–19 years
Owoeye et al[20]	2006	Nigeria	20	Proptosis (85%)	35%	—
Saiju et al[39]	2006	Nepal	30	Leukocoria (43%)	—	—
Mukhopadhyay et al[40]	2006	India	21	Leukocoria (86%)	—	—
Chang et al[41]	2006	Taiwan	54	Leukocoria (71%)	81%	2–264 months
Ozkan et al[42]	2006	Turkey	141	Leukocoria (82%)	92%	2–132 months
Ozdemir et al[43]	2007	Turkey	91	Leukocoria (65%)	92%	4–63 months
Chung et al[15]	2008	Korea	70	Leukocoria (80%)	100%	7–65 months
Bowman et al[44]	2008	Tanzania	91	—	23%	0–40 months
Swaminathan et al[45]	2008	India	82	—	48%	5 years
MacCarthy et al[29]	2009	Great Britain	1,576	—	97% for unilateral cases 100% for bilateral cases	5 years
Broaddus et al[46]	2009	USA	992	—	97%	5 years
Naseripour et al[14]	2009	Iran	105	Leukocoria (65%)	83%	3–72 months
Gupta et al[47]	2009	India'	140	Leukocoria (84%)	—	—
Reddy and Anusya[48]	2010	Malaysia	64	Leukocoria (72%)	—	6 months–9.5 years
Essuman et al[49]	2010	Ghana	23	Leukocoria (87%)	26%	1 day–19 months
Ali et al[50]	2011	Sudan	25	Enlarged eye (56%)	36%	9–36 months
Zhao et al[23]	2011	China	470	Leukocoria (73%)	—	—
Bai et al[24]	2011	China	1,234	Leukocoria (67%)	—	—
Abdu et al[33]	2011	Nigeria	42	Fungating mass (46%)	—	—
Chitsike et al[19]	2012	Zimbabwe	196	Proptosis (65%)	—	—
Navo et al[22]	2012	Argentina	508	Leukocoria (86%)	91%	12–240 months
Nabie et al[51]	2012	Iran	40	Leukocoria (98%)	—	—
Sah et al[17]	2013	Nepal	42	Extraocular tumor (29%)	24%	10 years
Lim et al[18]	2013	Singapore	51	Leukocoria (71%)	91%	0–13 years
Saiju et al[25]	2013	Nepal	30	Leukocoria (80%)	—	—
Gündüz et al[52]	2013	Turkey	192	—	90%	1–171 months
Chebbi et al[12]	2014	Tunisia	200	Leukocoria (80%)	—	—
Subramaniam et al[53]	2014	Malaysia	119	Leukocoria (92%)	55%	1 year

(*continued on next page*)

Table 8. (*Continued*)

Authors	Year of Publication	Study Place	No. of Patients	Most Common Presenting Complaint	Patient Survival Rate	Follow-up Period
Kruger et al[54]	2014	South Africa	51	—	33% (before outreach interventions) and 43% (after outreach interventions)	5 years
Waddell et al[55]	2014	Uganda	270	—	45% (before introduction of chemotherapy) and 65% (after introduction of chemotherapy)	35 months
Al-Nawaiseh et al[56]	2014	Jordan	71	Leukocoria (54%)	99%	0.25–160 months
Moreno et al[57]	2014	Argentina	438	—	89%	3 years
Wiangnon et al[58]	2014	Thailand	—	—	55%	5 years
da Rocha-Bastos et al[59]	2014	Portugal	46	Leukocoria (37%)	98%	1–33 years
Park et al[60]	2014	Korea	600	—	92%	10 years
El Kettani et al[61]	2014	Morocco	32	Leukocoria (69%)	87%	52 months
Luo et al[62]	2015	China	314	Leukocoria (77%)	81%	1–110 months
Asencio-López et al[63]	2015	Mexico	108	Leukocoria (86%)	92%	200 months
Gichigo et al[64]	2015	Kenya	160	—	27%	1–144 months
Wongmas et al[65]	2015	Thailand	75	—	60%	—
Lumbroso-Le Rouic et al[66]	2015	France	730	—	98.5%	93 months
Chang et al[67]	2015	China	47	Decreased vision (43%)	100%	0.2–9.8 years
Waddell et al[68]	2015	Uganda	282	—	47%	1–86 months
Okimoto et al[69]	2015	Japan	34	Leukocoria (97%)	97%	1 year
El Zomor et al[70]	2015	Egypt	262	Leukocoria (74%)	—	—
Chawla et al[3]	2015	India	600	Leukocoria (83%)	76%	1–60 months
Selistre et al[71]	2016	Brazil	140	Leukocoria (74%)	86%	300–346 months
Gao et al[72]	2016	China	253	Leukocoria (71%)	91%	0.3–119 months
Li et al[73]	2016	Taiwan	154	—	83%	2 years
Jin et al[74]	2017	China	436	Leukocoria (79%)	99%	0.5–21 months
Soliman et al[75]	2017	Egypt	47	Leukocoria (96%)	100%	—
Al Hasan et al[76]	2017	Syria	37	Leukocoria (57%)	—	—
Present study	2017	India	1,457	Leukocoria (75%)	92%	3–234 months

and external beam radiotherapy (45–50 Gy) was given in all cases.[82]

The survival rate of patients with RB is excellent in developed nations compared with developing nations.[30] The estimated disease-related mortality is highest in Africa (70%) and Asia (39%), because of advanced disease at presentation.[30] Based on published literature, the survival rates are summarized in Table 8.[3,8,12–20,22–27,29,33, 35–76] In our study, it was noted that the survival rate in Asian Indian patients with RB is favorable with appropriate treatment. The 5-year and 10-year survival estimates by Kaplan–Meier analysis was 90% and 89%, respectively. Among the patients who died of RB, the mean age at diagnosis was 44 months, and 69% patients had extraocular tumor extension at presentation, indicating a delayed diagnosis as the main cause of mortality in these patients. Our analysis of 80 patients with Stage III or Stage IV disease at presentation revealed survival rate of 71% in patients presenting with Stage III disease and 0% in those with Stage IV disease.[82]

Based on our analysis, there was no difference in the clinical presentation and outcome based on geographic distribution. However, based on disease laterality, significant differences were noted. Bilateral cases were younger at presentation and had a higher rate of positive family history of RB. Because of earlier presentation, the tumors were mostly intraocular with lower tumor grouping and staging, and fewer cases needed primary enucleation compared with unilateral cases. These findings suggest that there is a correlation between age at presentation and stage of disease,[83] which ultimately affects the globe salvage rates.

On comparison of our study with other studies from India, the most common presenting complaint was leukocoria and was comparable to other studies.[3,8,40,47] In our study, the survival rate was 92%. In a study of 82 children with RB, the 5-year survival rate was reported as 48%.[45] Low survival rate in this study could be related to referral bias because all cases in that study were those who were treated at a regional general oncology center rather than an ocular oncology center.[45] In a study of 600 children with RB,[3] the survival rate was 76%. However, in their study, there was higher number of cases with extraocular tumor extension on presentation (28%), which contributed to higher death rate compared with our study.[3] In other study of 355 children with RB, the survival rate was better at 99%; however, the validity of the outcome is limited because of relatively short follow-up duration.[8]

Based on our data analysis in three 5-year periods, the age at presentation of RB especially in the female children is improving (30 months in 2000–2005 and 27 months in 2011–2015; $P = 0.04$), less common presenting complaints of RB-like strabismus are increasing (3% in 2000–2005 and 8% in 2011–2015; $P = 0.02$), orbital tumor extension at presentation are decreasing (12% in 2000–2005 and 7% in 2011–2015; $P = 0.01$), tumor diagnosis at early stage are increasing (ICIoR Group C, 4% in 2000–2005 and 7% in 2011–2015; $P = 0.03$; ICIoR Group D, 20% in 2000–2005 and 17% in 2011–2015; $P = 0.02$; and IRSS Stage III, 9% in 2000–2005 and 4% in 2011–2015; $P = 0.001$), with increased rates of globe salvage (IRSS Stage 0, 37% in 2000–2005 and 49% in 2011–2015; $P = 0.01$), increased rate of systemic chemotherapy as primary treatment (41% in 2000–2005 and 62% in 2011–2015; $P < 0.001$), decreased rates of primary enucleation (50% in 2000–2005 and 31% in 2011–2015; $P < 0.001$), and decreased rates of treatment denial (14% in 2000–2005 and 5% in 2011–2015; $P < 0.001$).

In conclusion, the age at presentation of RB in India is much higher compared with developed nations. The most common presenting complaints are leukocoria and proptosis as against leukocoria and strabismus in developed nations. The presence of extraocular tumor extension of RB at presentation is common in Asian Indian patients compared with the west. Despite the advanced disease at presentation, with appropriate treatment, the survival rates are comparable to the developed nations. In the coming years, with increased awareness about the disease among the public especially the parents and grandparents, general physicians, and pediatricians and improved accessibility to appropriate treatment especially in rural areas can further improve the survival and globe salvage rates in children with RB in India.

Key words: eye, retina, retinoblastoma, India.

References

1. Usmanov RH, Kivelä T. Predicted trends in the incidence of retinoblastoma in the Asia-Pacific region. Asia Pac J Ophthalmol (Phila) 2014;3:151–157.
2. Rangamani S, SathishKumar K, Manoharan N, et al. Paediatric retinoblastoma in India: evidence from the National Cancer Registry Programme. Asian Pac J Cancer Prev 2015;16: 4193–4198.
3. Chawla B, Hasan F, Azad R, et al. Clinical presentation and survival of retinoblastoma in Indian children. Br J Ophthalmol 2016;100:172–178.
4. Kaliki S, Srinivasan V, Gupta A, et al. Clinical features predictive of high-risk retinoblastoma in 403 Asian Indian patients: a case-control study. Ophthalmology 2015;122:1165–1172.
5. Shah PK, Narendran V, Kalpana N. Outcomes of intra and extraocular retinoblastomas from a single institute in South India. Ophthalmic Genet 2015;36:248–250.
6. Sachdeva S. Trend of reported cases of retinoblastoma under five hospital based cancer registries. Indian J Cancer 2010;47: 473–474.

7. Arora RS, Eden TO, Kapoor G. Epidemiology of childhood cancer in India. Indian J Cancer 2009;46:264–273.
8. Shanmugam MP, Biswas J, Gopal L, et al. The clinical spectrum and treatment outcome of retinoblastoma in Indian children. J Pediatr Ophthalmol Strabismus 2005;42:75–81.
9. Sahu S, Banavali SD, Pai SK, et al. Retinoblastoma: problems and perspectives from India. Pediatr Hematol Oncol 1998;15: 501–508.
10. Dhir SP, Jain IS, Dar GR, Gupta HD. Survival of retinoblastoma cases in North India. Indian J Ophthalmol 1981;29:447–450.
11. Shrikhande SS, Sirsat MV. Retinoblastoma in Indians. Indian J Cancer 1966;3:57–68.
12. Chebbi A, Bouguila H, Boussaid S, et al. Clinical features of retinoblastoma in Tunisia. J Fr Ophtalmol 2014;37:442–448.
13. Kao LY, Su WW, Lin YW. Retinoblastoma in Taiwan: survival and clinical characteristics 1978-2000. Jpn J Ophthalmol 2002;46:577–580.
14. Naseripour M, Nazari H, Bakhtiari P, et al. Retinoblastoma in Iran: outcomes in terms of patients' survival and globe survival. Br J Ophthalmol 2009;93:28–32.
15. Chung SE, Sa HS, Koo HH, et al. Clinical manifestations and treatment of retinoblastoma in Korea. Br J Ophthalmol 2008; 92:1180–1184.
16. Kaimbo WK, Mvitu MM, Missotten L. Presenting signs of retinoblastoma in Congolese patients. Bull Soc Belge Ophtalmol 2002;283:37–41.
17. Sah KP, Saiju R, Roy P, Kafle S. Retinoblastoma: ten years experience at Kanti Children's Hospital. JNMA J Nepal Med Assoc 2013;52:576–579.
18. Lim FP, Soh SY, Iyer JV, et al. Clinical profile, management, and outcome of retinoblastoma in Singapore. J Pediatr Ophthalmol Strabismus 2013;50:106–112.
19. Chitsike I, Kuona P, Dzangare J, et al. Patterns of retinoblastoma in Zimbabwe: 2000-2009. Cent Afr J Med 2012;58:1–5.
20. Owoeye JF, Afolayan EA, Ademola-Popoola DS. Retinoblastoma—a clinico-pathological study in Ilorin, Nigeria. Afr J Health Sci 2006;13:117–123.
21. Akang EE, Ajaiyeoba IA, Campbell OB, et al. Retinoblastomas in Ibadan Nigeria: II—clinicopathologic features. West Afr J Med 2000;19:6–11.
22. Navo E, Teplisky D, Albero R, et al. Clinical presentation of retinoblastoma in a middle-income country. J Pediatr Hematol Oncol 2012;34:e97–e101.
23. Zhao J, Li S, Shi J, Wang N. Clinical presentation and group classification of newly diagnosed intraocular retinoblastoma in China. Br J Ophthalmol 2011;95:1372–1375.
24. Bai S, Ren R, Shi J, et al. Retinoblastoma in the Beijing Tongren Hospital from 1957 to 2006: clinicopathological findings. Br J Ophthalmol 2011;95:1072–1076.
25. Saiju R, Moore G, Shrestha U, et al. Retinoblastoma: geographic distribution and presentation at a tertiary eye care centre in Kathmandu, Nepal. Nepal J Ophthalmol 2013;5:169–176.
26. Badhu B, Sah SP, Thakur SK, et al. Clinical presentation of retinoblastoma in Eastern Nepal. Clin Exp Ophthalmol 2005; 33:386–389.
27. Abramson DH, Frank CM, Susman M, et al. Presenting signs of retinoblastoma. J Pediatr 1998;132:505–508.
28. Abramson DH, Ellsworth RM, Grumbach N, Kitchin FD. Retinoblastoma: survival, age at detection and comparison 1914-1958, 1958-1983. J Pediatr Ophthalmol Strabismus 1985;22: 246–250.
29. MacCarthy A, Birch JM, Draper GJ, et al. Retinoblastoma: treatment and survival in Great Britain 1963 to 2002. Br J Ophthalmol 2009;93:38–39.
30. Kivelä T. The epidemiological challenge of the most frequent eye cancer: retinoblastoma, an issue of birth and death. Br J Ophthalmol 2009;93:1129–1131.
31. Shields CL, Mashayekhi A, Demirci H, et al. Practical approach to management of retinoblastoma. Arch Ophthalmol 2004;122:729–735.
32. Chantada G, Doz F, Antoneli CB, et al. A proposal for an international retinoblastoma staging system. Pediatr Blood Cancer 2006;47:801–805.
33. Abdu L, Malami S. Clinicopathological pattern and management of retinoblastoma in Kano, Nigeria. Ann Afr Med 2011; 10:214–219.
34. Boubacar T, Fatou S, Fousseyni T, et al. A 30-month prospective study on the treatment of retinoblastoma in the Gabriel Toure Teaching Hospital, Bamako, Mali. Br J Ophthalmol 2010;94:467–469.
35. Günalp I, Gündüz K, Arslan Y. Retinoblastoma in Turkey—treatment and prognosis. Jpn J Ophthalmol 1996;40:95–102.
36. Saw SM, Tan N, Lee SB, et al. Incidence and survival characteristics of retinoblastoma in Singapore from 1968-1995. J Pediatr Ophthalmol Strabismus 2000;37:87–93.
37. Sant M, Capocaccia R, Badioni V. UROCARE working group. Survival for retinoblastoma in Europe. Eur J Cancer 2001;37: 730–735.
38. Leal-Leal C, Flores-Rojo M, Medina-Sansón A, et al. A multicentre report from the Mexican retinoblastoma group. Br J Ophthalmol 2004;88:1074–1077.
39. Saiju R, Thakur J, Karmacharya PC, Shah DN. Retinoblastoma in Nepal: a clinical profile of 30 cases. Nepal Med Coll J 2006; 8:171–175.
40. Mukhopadhyay S, Ghosh S, Chattopadhyay D, Dutta SK. An observational study on retinoblastoma cases attending a medical college in Calcutta. J Indian Med Assoc 2006;104:67–70.
41. Chang CY, Chiou TJ, Hwang B, et al. Retinoblastoma in Taiwan: survival rate and prognostic factors. Jpn J Ophthalmol 2006;50:242–249.
42. Ozkan A, Pazarli H, Celkan T, et al. Retinoblastoma in Turkey: survival and clinical characteristics 1981-2004. Pediatr Int 2006;48:369–373.
43. Ozdemir H, Tacyildiz N, Unal E, et al. Clinical and epidemiological characteristics of retinoblastoma: correlation with prognosis in a Turkish pediatric oncology center. Pediatr Hematol Oncol 2007;24:221–231.
44. Bowman RJ, Mafwiri M, Luthert P, et al. Outcome of retinoblastoma in east Africa. Pediatr Blood Cancer 2008;50:160–162.
45. Swaminathan R, Rama R, Shanta V. Childhood cancers in Chennai, India, 1990-2001: incidence and survival. Int J Cancer 2008;122:2607–2611.
46. Broaddus E, Topham A, Singh AD. Survival with retinoblastoma in the USA: 1975-2004. Br J Ophthalmol 2009;93:24–27.
47. Gupta R, Vemuganti GK, Reddy VA, Honavar SG. Histopathologic risk factors in retinoblastoma in India. Arch Pathol Lab Med 2009;133:1210–1214.
48. Reddy SC, Anusya S. Clinical presentation of retinoblastoma in Malaysia: a review of 64 patients. Int J Ophthalmol 2010;3: 64–68.
49. Essuman V, Ntim-Amponsah CT, Akafo S, et al. Presentation of retinoblastoma at a paediatric eye clinic in Ghana. Ghana Med J 2010;44:10–15.

50. Ali AA, Elsheikh SM, Elhaj A, et al. Clinical presentation and outcome of retinoblastoma among children treated at the National Cancer Institute (NCI) in Gezira, Sudan: a single institution experience. Ophthalmic Genet 2011;32:122–125.
51. Nabie R, Taheri N, Fard AM, Fouladi RF. Characteristics and clinical presentations of pediatric retinoblastoma in Northwestern Iran. Int J Ophthalmol 2012;5:510–512.
52. Gündüz K, Köse K, Kurt RA, et al. Retinoblastoma in Turkey: results from a tertiary care center in Ankara. J Pediatr Ophthalmol Strabismus 2013;50:296–303.
53. Subramaniam S, Rahmat J, Rahman NA, et al. Presentation of retinoblastoma patients in Malaysia. Asian Pac J Cancer Prev 2014;15:7863–7867.
54. Kruger M, Reynders D, Omar F, et al. Retinoblastoma outcome at a single institution in South Africa. S Afr Med J 2014;104:859–863.
55. Waddell KM, Kagame K, Ndamira A, et al. Improving survival of retinoblastoma in Uganda. Br J Ophthalmol 2015;99:937–942.
56. Al-Nawaiseh I, Jammal HM, Khader YS, et al. Retinoblastoma in Jordan, 2003-2013: ocular survival and associated factors. Ophthalmic Epidemiol 2014;21:406–411.
57. Moreno F, Sinaki B, Fandiño A, et al. A population-based study of retinoblastoma incidence and survival in Argentine children. Pediatr Blood Cancer 2014;61:1610–1615.
58. Wiangnon S, Jetsrisuparb A, Komvilaisak P, Suwanrungruang K. Childhood cancer incidence and survival 1985-2009, Khon Kaen, Thailand. Asian Pac J Cancer Prev 2014;15:7989–7993.
59. da Rocha-Bastos R, Araújo J, Silva R, et al. Retinoblastoma: experience of a referral center in the North Region of Portugal. Clin Ophthalmol 2014;8:993–997.
60. Park SJ, Woo SJ, Park KH. Incidence of retinoblastoma and survival rate of retinoblastoma patients in Korea using the Korean National Cancer Registry database (1993-2010). Invest Ophthalmol Vis Sci 2014;55:2816–2821.
61. El Kettani A, Aderdour S, Daghouj G, et al. Retinoblastoma: preliminary results of national treatment protocol at Casablanca university medical center. J Fr Ophtalmol 2014;37:115–124.
62. Luo X, Ye H, Ding YG, et al. Clinical characteristics and prognosis of patients with retinoblastoma: 8-year follow-up. Turk J Med Sci 2015;45:1256–1262.
63. Asencio-López L, Torres-Ojeda AA, Isaac-Otero G, Leal-Leal CA. Treating retinoblastoma in the first year of life in a national tertiary paediatric hospital in Mexico. Acta Paediatr 2015;104:e384–e387.
64. Gichigo EN, Kariuki-Wanyoike MM, Kimani K, Nentwich MM. Retinoblastoma in Kenya: survival and prognostic factors. Ophthalmologe 2015;112:255–260.
65. Wongmas P, Jetsrisuparb A, Komvilaisak P, et al. Incidences, trends and long term outcomes of retinoblastoma in three cancer registries, Thailand. Asian Pac J Cancer Prev 2015;16:6899–6902.
66. Lumbroso-Le Rouic L, Savignoni A, Levy-Gabriel C, et al. Treatment of retinoblastoma: the Institut Curie experience on a series of 730 patients (1995 to 2009). J Fr Ophtalmol 2015;38:535–541.
67. Chang Y, Shi J, Zhao J, et al. Retinoblastoma in Chinese children aged five to fourteen years. Ophthalmologica 2015;233:222–229.
68. Waddell KM, Kagame K, Ndamira A, et al. Clinical features and survival among children with retinoblastoma in Uganda. Br J Ophthalmol 2015;99:387–390.
69. Okimoto S, Nomura K. Clinical manifestations and treatment of retinoblastoma in Kobe children's hospital for 16 years. J Pediatr Ophthalmol Strabismus 2014;51:222–229.
70. El Zomor H, Nour R, Alieldin A, et al. Clinical presentation of intraocular retinoblastoma; 5-year hospital-based registry in Egypt. J Egypt Natl Canc Inst 2015;27:195–203.
71. Selistre SG, Maestri MK, Santos-Silva P, et al. Retinoblastoma in a pediatric oncology reference center in Southern Brazil. BMC Pediatr 2016;16:48.
72. Gao J, Zeng J, Guo B, et al. Clinical presentation and treatment outcome of retinoblastoma in children of South Western China. Medicine (Baltimore) 2016;95:e5204.
73. Li SY, Chen SC, Tsai CF, et al. Incidence and survival of retinoblastoma in Taiwan: a nationwide population-based study 1998-2011. Br J Ophthalmol 2016;100:839–842.
74. Jin L, Zhang W, Pan H, et al. Retrospective investigation of retinoblastoma in Chinese patients. Oncotarget 2017 Epub ahead of print.
75. Soliman SE, Eldomiaty W, Goweida MB, Dowidar A. Clinical presentation of retinoblastoma in Alexandria: a step toward earlier diagnosis. Saudi J Ophthalmol 2017;31:80–85.
76. Al Hasan A, Murad R, Zaid KH, et al. Epidemiological characteristics of retinoblastoma in children attending Almouassat University Hospital, Damascus, Syria, 2012-2016. Asian Pac J Cancer Prev 2017;18:421–424.
77. Shields JA, Shields CL. Retinoblastoma: introduction, genetics, clinical features, classification. In: Shields JA, Shields CL, eds. Intraocular Tumors: An Atlas and Textbook. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2008:294–300.
78. Faranoush M, Hedayati Asl AA, Mehrvar A, et al. Consequences of delayed diagnosis in treatment of retinoblastoma. Iran J Pediatr 2014;24:381–386.
79. Chantada G, Schaiquevich P. Management of retinoblastoma in children: current status. Paediatr Drugs 2015;17:185–198.
80. Kaliki S, Shields CL. Retinoblastoma: achieving new standards with methods of chemotherapy. Indian J Ophthalmol 2015;63:103–109.
81. Abramson DH, Shields CL, Munier FL, Chantada GL. Treatment of retinoblastoma in 2015: agreement and disagreement. JAMA Ophthalmol 2015;133:1341–1347.
82. Kaliki S, Patel A, Iram S, Palkonda VAR. Clinical presentation and outcomes of stage III or stage IV retinoblastoma in 80 Asian Indian patients. J Pediatr Ophthalmol Strabismus 2017;54:177–184.
83. Rubenfeld M, Abramson DH, Ellsworth RM, Kitchin FD. Unilateral vs. bilateral retinoblastoma. Correlations between age at diagnosis and stage of ocular disease. Ophthalmology 1986;93:1016–1019.