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HIGH-RISK HISTOPATHOLOGICAL FEATURES OF RETINOBLASTOMA FOLLOWING PRIMARY ENUCLEATION

A Global Study Of 1,426 Patients From 5 Continents

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Purpose: To evaluate high-risk histopathological features following primary enucleation of eyes with retinoblastoma and assess the patient outcomes across continents.

Methods: A retrospective study of 1,426 primarily enucleated retinoblastoma eyes from five continents.

Results: Of all, 923 (65%) were from Asia (AS), 27 (2%) from Australia (AUS), 120 (8%) from Europe (EUR), 162 (11%) from North America (NA), and 194 (14%) from South America (SA). Based on the continent (AS vs. AUS vs. EUR vs. NA vs. SA), the histopathological features included massive choroidal invasion (31% vs. 7% vs. 13% vs. 19% vs. 27%, $P = 0.001$), postlaminar optic nerve invasion (27% vs. 0% vs. 16% vs. 21% vs. 19%, $P = 0.0006$), scleral infiltration (5% vs. 0% vs. 4% vs. 2% vs. 7%, $P = 0.13$), and microscopic extrascleral infiltration (4% vs. 0% vs. $<1\%$ vs. $<1\%$ vs. 4%, $P = 0.68$). Adjuvant chemotherapy with/without orbital radiotherapy was given to 761 (53%) patients. Based on Kaplan–Meier estimates in different continents (AS vs. AUS vs. EUR vs. NA vs. SA), the 6-year risk of orbital tumor recurrence was 5% versus 2% versus 0% versus 0% versus 12% ($P < 0.001$), systemic metastasis was reported in 8% versus 5% versus 2% versus 0% versus 13% ($P = 0.001$), and death in 10% versus 3% versus 2% versus 0% versus 11% ($P < 0.001$) patients.

Conclusion: There is a wide variation in the infiltrative histopathological features of retinoblastoma across continents, resulting in variable outcomes. SA and AS had a higher risk of orbital tumor recurrence, systemic metastasis, and death compared to AUS, EUR, and NA.

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In the late 1950s, Carbajal[1] documented certain histopathological findings in the enucleated eyes of retinoblastoma (RB), which "signify gravity of the disease" and aid in prognostication. Over time, as the therapy of RB evolved, these histopathological findings and criteria were accepted, refuted, debated, revised, and eventually evolved into what is now known as "high-risk histopathological features (HRHFs)" of RB.[2] Despite some heterogeneity in defining HRHFs, the most widely accepted criteria include massive choroidal infiltration, postlaminar optic nerve infiltration, optic nerve transection involvement, and extrascleral tissue infiltration.[2–4] The use of adjuvant chemotherapy regimens in patients with HRHF has been suggested to lower the risk of local recurrence, metastasis, and death from RB in patients with HRHF.[5]

Global studies on RB have shown that the clinical presentation and outcomes of RB are affected by age at presentation, lag time from symptom onset to presentation, country income status, tumor laterality, heredity, and genetic basis.[6–11] The pathological signature of tumors is the bridge that connects the clinico-demographic variables to disease outcomes. However, histopathological features and the presence of HRHFs, which greatly affect the survival in RB, have not been extensively studied. First, how commonly are HRHFs encountered worldwide? These data are highly variable, ranging from 23% to 78% of enucleated RB eyes in various studies.[12–17] Second, does the tumor histomorphology differ by region, race, and ethnicity? These data are lacking, with only a few intercontinental studies that focused on this aspect.[16,17] This multicenter intercontinental collaborative study explores these important questions and attempts to bridge the knowledge gaps in the literature.

Methods

Treatment centers across six (Asia, Africa, Australia, Europe, North America, and South America) continents were invited to participate in a multicenter, retrospective, collaborative study focusing on the HRHFs of RB in patients who underwent primary enucleation from 2011 to 2020. Centers from five (Asia, Australia, Europe, North America, and South America) continents agreed to participate and formed the "High-risk Retinoblastoma Collaborative Study Group". The availability of accurately documented histopathological data was a mandate. Information was provided by all the participating centers on the demographics (age, sex, gender, race, heredity, laterality), clinical features (presenting

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complaints, ocular examination, tumor group by the International Classification of Retinoblastoma [ICRB][18] and the International Intraocular Retinoblastoma Classification [IIRC],[19] tumor stage by the 8th edition of the American Joint Committee on Cancer [AJCC]),[18] histopathological features (growth pattern, tumor differentiation, involvement of ocular structures, HRHFs, pTNM stage),[20] treatment details (enucleation, adjuvant chemotherapy, radiotherapy), and outcomes (orbital tumor recurrence, systemic metastasis, tumor-related death). All the aforementioned data, including the grouping and staging of RB, were based on the physical and medical records, fundus cartograms, and pathology reports. For the HRHFs, all features presumed as high risk for systemic metastasis described in the literature were looked for. As it was a retrospective study, the definition of HRHFs was variable between centers.

The study cohort was divided into groups based on the continent of origin: Asia (AS: Bangladesh, India, Israel, Japan, Jordan, Pakistan), Australia (AUS), Europe (EUR: Russia, United Kingdom), North America (NA: United States of America), and South America (SA: Peru), and the various parameters and outcomes were compared between the subgroups.

The study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[21] The participating centers obtained approval from the respective individual ethics committees. The study was conducted in adherence to the tenets of the Declaration of Helsinki.

Data Collection

A Microsoft Excel spreadsheet was designed after deliberation with the lead ocular oncologists at the participating centers and circulated to all centers. The data were entered by medical students, residents, and postdoctoral fellows, who received a short training session on data entry in the spreadsheet. The lead ocular oncologists monitored the accuracy of the data entry at periodic intervals and at the culmination of data collection. SK was responsible for the accurate compilation of data from all centers and further statistical analysis.

Statistical Analysis

The demographics, clinical features, histopathological features, treatment details, and outcomes were compared between these groups. The statistical analysis was performed using R software (version 4.3.2). Descriptive data were summarized as mean, median, range, and proportion. Continuous data were compared using analysis of variance (ANOVA), and categorical data were compared using the Chi-square test. A P-value of <0.05 was considered statistically significant where in one-to-one comparisons were made between the continent groups. Post hoc analysis of continuous data was performed using the Bonferroni test. Cox proportional hazards regression was used to estimate the impact of the continent of origin on the outcomes. Kaplan–Meier estimates were used to predict the rates of local recurrence, metastasis, and death between different continents at 3 months, 6 months, 1 year, 2 years, 3 years, and 6 years.

Results

There were 21 centers from 11 countries across 5 continents that participated in the study and enrolled a total of 1,426 eyes in 1,426 patients. The participating centers, being recognized as RB treatment centers, largely reflected the national estimates of the country of origin. A majority of patients were enrolled from Asia (n = 923, 65%), followed by South America (n = 194, 14%), North America (n = 162, 11%), Europe (n = 120, 8%), and Australia (n = 27, 2%). The North American continent was represented by the United States and the South American continent by Peru. No patients could be enrolled from Africa.

Demographics and Clinical Features

The demographic and clinical details of patients are listed in Table 1 and Table 2, respectively. The mean age at the time of diagnosis of RB was 30 months (median, 26 months; range, 11–143 months). Data on grouping by the ICRB and IIRC systems were available for 1,405 (99%) and 1,312 (92%) patients, respectively. A majority of enucleated eyes belonged to ICRB Group E in AS (n = 813, 88%), AUS (n = 22, 81%), EUR (n = 106, 88%), NA (n = 139, 97%), and SA (n = 114, 59%). However, a sizeable number of enucleated eyes belonged to ICRB Group D in SA (n = 80, 41%), compared with AS (n = 105, 11%), AUS (n = 5, 19%), EUR (n = 14, 12%), and NA (n = 5, 3%). Only 2 (<1%) Group C eyes were enucleated, and both belonged to patients with unilateral RB from AS.

Histopathological Features

1. Tumor growth pattern and degree of differentiation

Details of tumor growth pattern and tumor differentiation were available in 1,342 (94%) and 1,366 (96%) of the 1,426 enucleated eyes, respectively. Endophytic growth was the most common pattern seen on histopathological examination, in 642 (48%) eyes. Eyes from AS, EUR, and SA displayed endophytic tumors in a majority (48%, 56%, and 62%

Table 1. Demographics of 1,426 Retinoblastoma Patients From Five Continents Who Underwent Primary Enucleation

Feature	All Cases, n = 1,426, n (%)	Asia, n = 923, n (%)	Australia, n = 27, n (%)	Europe, n = 120, n (%)	North America, n = 162, n (%)	South America, n=194, n (%)	*P*
Age at presentation (months) Mean (median, range)	30 (26, 11–143)	31 (26, 11–120)	23 (21, 6–63)	28 (25, 1–120)	28 (23, <1–143)	29 (27, 1–98)	0.2162
Sex							
Male	757 (53)	510 (55)	10 (37)	63 (53)	74 (46)	100 (52)	0.08102
Female	668 (47)	412 (45)	17 (63)	57 (48)	88 (54)	94 (48)	0.07542
Race							
Caucasian	135 (10)	23 (3)	18 (67)	12 (10)	82 (51)	0 (0)	<0.001*
African American	29 (2)	1 (<1)	0 (0)	0 (0)	28 (55)	0 (0)	<0.001†
Asian	841 (59)	809 (88)	4 (15)	12 (10)	16 (10)	0 (0)	<0.001‡
Hispanic	226 (16)	0 (0)	0 (0)	0 (0)	32 (20)	194 (100)	<0.001§
Arab	96 (7)	90 (10)	4 (15)	0 (0)	2 (1)	0 (0)	0.001¶
African	2 (<1)	0 (0)	0 (0)	0 (0)	2 (1)	0 (0)	0.003563
British	20 (1)	0 (0)	0 (0)	20 (17)	0 (0)	0 (0)	<0.001**
Russian	76 (5)	0 (0)	0 (0)	76 (63)	0 (0)	0 (0)	<0.001††
Indigenous Australian	1 (<1)	0 (0)	1 (4)	0 (0)	0 (0)	0 (0)	0.001‡‡
Hereditary pattern							
Sporadic	1,345 (94)	874 (95)	27 (100)	118 (98)	132 (81)	194 (100)	0.001§§
Familial	78 (6)	46 (5)	0 (0)	2 (2)	30 (19)	0 (0)	0.001¶¶
Tumor laterality							
Unilateral	1,204 (84)	746 (81)	25 (93)	116 (97)	134 (83)	183 (94)	0.001***
Bilateral	222 (6)	177 (19)	2 (7)	4 (3)	28 (17)	11 (6)	0.001†††
Duration of symptoms (months) Mean (median, range)	4 (2, <1–51)	4 (2, <1–51)	2 (1, <1–12)	3 (1, <1–25)	3 (1, <1–36)	5 (3, <1–36)	0.002‡‡‡

*Post hoc analysis showed that AS was significantly different from AUS, EU, and NA; AUS was significantly different from EU and SA; EU was significantly different from NA and SA; NA was significantly different from SA.

†Post hoc analysis showed that AS was significantly different from NA; EU was significantly different from NA; NA was significantly different from SA.

‡Post hoc analysis showed that AS was significantly different from AUS, EU, NA, and SA; AUS was significantly different from SA; EU was significantly different from SA; NA was significantly different from SA.

§Post hoc analysis showed that AS was significantly different from NA and SA; AUS was significantly different from SA; EU was significantly different from NA and SA; NA was significantly different from SA.

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**Post hoc analysis showed that AS was significantly different from EU; EU was significantly different from NA and SA.

††Post hoc analysis showed that AS was significantly different from EU; AUS was significantly different from EU; EU was significantly different from NA and SA.

‡‡Post hoc analysis showed that AS was significantly different from AUS.

§§Post hoc analysis showed that AS was significantly different from NA and SA; EU was significantly different from NA; NA was significantly different from SA.

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***Post hoc analysis showed that AS was significantly different from AUS and SA; EU was significantly different from NA; NA was significantly different from SA.

†††Post hoc analysis showed that AS was significantly different from EU and SA; EU was significantly different from NA; NA was significantly different from SA.

‡‡‡Post hoc analysis showed that SA was significantly different from NA and EU.

Table 2. Clinical Features at Presentation of 1,426 Retinoblastoma Patients From Five Continents Who Underwent Primary Enucleation

Feature	All Cases, n = 1,426, n (%)	Asia, n = 923, n (%)	Australia, n = 27, n (%)	Europe, n = 120, n (%)	North America, n = 162, n (%)	South America, n = 194, n (%)	*P*
Horizontal corneal diameter (mm) Mean (median, range)	12 (12, 8–15)	12 (12, 8–15)	14 (14, 14)	11 (11, 9–13)	12 (12, 10–14)	Na	0.001*
Megalocornea (n=1,054)	85 (8)	65 (8)	1 (4)	3 (3)	16 (10)	Na	0.0002562†
Intraocular pressure (mmHg) Mean (median, range)	19 (13, 0–65)	18 (12, 0–65)	27 (26, 8–55)	18 (12, 4–48)	25 (21, 5–62)	Na	<0.001‡
Secondary glaucoma (n=1,047)	342 (33)	233 (30)	4 (15)	39 (33)	66 (49)	Na	<0.001§
Anterior chamber seeds (n=1,421)	138 (10)	107 (12)	1 (4)	13 (11)	8 (5)	9 (5)	0.004795¶
Neovascularization of iris (n=1,415)	353 (25)	223 (24)	5 (19)	50 (42)	74 (46)	1 (<1)	<0.001**
Hyphema (n=1,419)	69 (5)	54 (6)	0 (0)	2 (2)	3 (2)	10 (5)	0.05565
Ectropion uveae (n=1,421)	160 (11)	132 (14)	0 (0)	7 (6)	21 (13)	0 (0)	<0.001††
Cataract (n=1,419)	70 (5)	59 (6)	0 (0)	4 (3)	5 (3)	2 (1)	0.008012‡‡
Orbital pseudocellulitis	51 (4)	46 (5)	0 (0)	3 (3)	2 (1)	0 (0)	0.002441§§
International classification of retinoblastoma (n=1,405)							
Group C	2 (<1)	2 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0.8956
Group D	209 (15)	105 (11)	5 (19)	14 (12)	5 (3)	80 (41)	<0.001¶¶
Group E	1,194 (85)	813 (88)	22 (81)	106 (88)	139 (97)	114 (59)	<0.001***
International classification of intraocular retinoblastoma (n=1,312)							
Group C	2 (<1)	2 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0.8956
Group D	264 (20)	129 (14)	16 (59)	15 (13)	24 (15)	80 (79)	<0.001†††
Group E	1,046 (80)	772 (86)	11 (41)	105 (88)	137 (95)	21 (21)	<0.001‡‡‡
8th edition of AJCC (n=1,291)							
cT2b	572 (44)	262 (33)	19 (70)	44 (37)	87 (54)	160 (82)	<0.001§§§
cT3a	8 (<1)	6 (<1)	0 (0)	1 (<1)	0 (0)	1 (<1)	0.8504
cT3b	244 (19)	178 (23)	1 (4)	31 (26)	11 (7)	23 (12)	0.001¶¶¶
cT3c	280 (22)	186 (24)	7 (26)	32 (27)	55 (34)	0 (0)	0.001****
cT3d	82 (6)	61 (8)	0 (0)	5 (4)	6 (4)	10 (5)	0.3044
cT3e	47 (4)	43 (6)	0 (0)	3 (3)	1 (<1)	0 (0)	0.002118††††
cT4a	39 (3)	33 (4)	0 (0)	4 (3)	2 (1)	0 (0)	0.03724‡‡‡‡
cT4b	19 (2)	19 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0.03288

*Post hoc analysis showed that AS was significantly different from AUS and EU. NA was significantly different from EU and AUS; AUS was significantly different from EU.

†Post hoc analysis showed that AS was significantly different from SA; NA was significantly different from SA.

‡Post hoc analysis showed that AS was significantly different from AUS, EU, and NA; AUS was significantly different from EU, NA, and SA; EU was significantly different from SA; NA was significantly different from SA.

§Post hoc analysis showed that AS was significantly different from NA and SA; AUS was significantly different from NA and SA; EU was significantly different from SA; NA was significantly different from SA.

¶Post hoc analysis showed that AS was significantly different from SA.

**Post hoc analysis showed that AS was significantly different from EU, NA, and SA; AUS was significantly different from SA; EU was significantly different from SA; NA was significantly different from SA.

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§§§Post hoc analysis showed that AS was significantly different from AUS, NA, and SA; AUS was significantly different from EU; EU was significantly different from SA; NA was significantly different from SA.

¶¶¶Post hoc analysis showed that AS was significantly different from NA; EU was significantly different from NA and SA.

****Post hoc analysis showed that AS was significantly different from NA and SA; AUS was significantly different from SA; EU was significantly different from SA; NA was significantly different from SA.

††††Post hoc analysis showed that AS was significantly different from SA.

‡‡‡‡Post hoc analysis showed that AS was significantly different from SA.

respectively) ($P = 0.001$), whereas the exophytic pattern was more common in eyes from AUS (66%) and NA (40%) ($P = 0.001$).

The degree of tumor differentiation also displayed significant differences between the continents. Moderately differentiated tumors were the most common (n = 471, 34%) in the entire cohort and AS (n = 335, 37%). Poorly differentiated morphology was the most common type in NA (n = 81, 51%) and SA (n = 78, 44%), and undifferentiated morphology was the most common type in EUR (n = 57, 48%). Details of the degree of differentiation were unavailable in a majority (90%) of eyes from AUS.

2. Involvement of ocular structures, HRHFs, and pTNM staging

Histopathological details are listed in Table 3. In the entire cohort, the optic nerve (including prelamina, lamina, and postlamina) was the most common adjacent structure infiltrated by the tumor, with its involvement seen in 959 (67%) eyes. Eyes from AS displayed the highest proportion of iris (n = 91, 10%) and trabecular meshwork (n = 53, 6%) involvement ($P = 0.004$ and 0.02, respectively). Choroidal invasion of any extent was the highest in EUR (n = 85, 71%, $P = 0.001$), and the highest proportion of massive choroidal invasion was seen in AS (n = 283, n = 31%), followed by SA (n = 52, 27%). Optic nerve involvement was the highest in the EUR (n = 103, 86%) and the lowest in AUS (n = 4, 15%). Postlaminar optic nerve involvement was the highest in AS (n = 245, 27%), and involvement of the transected margin of the optic nerve was the highest in SA (n = 22, 11%).

Universally accepted HRHFs that were significantly different between the continents were as follows: massive choroidal invasion (AS (31%) vs. EUR (13%) vs. NA (19%), $P = 0.001$), postlaminar optic nerve invasion (AS (27%) vs. AUS (0%), $P = 0.0006$), and transected end of optic nerve (SA [11%] vs. EUR [0%], $P = 0.0007$). There were no significant differences between the continents in any form of scleral invasion. Among the equivocal HRHFs, iris invasion (AS [10%] vs. SA [3%], $P = 0.004412$), trabecular meshwork invasion (AS [6%] vs. SA [<1%], $P = 0.02035$), and the combination of prelaminar and minor choroidal invasion (AS [20%] vs. EUR [59%] and SA [32%], $P < 0.001$) were significantly different.

Nearly half (n = 655, 46%) of the 1,426 enucleated eyes were staged as AJCC stage pT1, that is, intraocular disease without any local invasion, focal choroidal invasion, or pre-/intralaminar optic nerve invasion. A majority of tumors belonged to the pT1 AJCC stage in AS (n = 420, 46%), AUS (n = 24, 89%), NA (n = 91, 56%), and SA (n = 83, 43%), whereas pT2a was the predominant pathological stage in EUR (n = 48, 40%). The advanced pT4 stage was more common in SA (n = 24, 12%), AS (n = 76, 8%), and NA (n = 9, 6%) than in EUR (n = 1, <1%) and AUS (n = 0, 0%). Differences in the tumor distribution in pT1, pT2a, and pT4 were significantly different between the continents.

Treatment and Outcomes

All 1,426 patients (100%) were treated with primary enucleation. The decision for adjuvant treatment was based on the individual center's definition of HRHFs, and this was significantly different between continents. Bilateral disease with an active tumor in the contralateral eye accounted for adjuvant treatment in children with HRHF-negative eyes (n = 60, 4%). Fifty-seven percent of patients in AS, 53% in SA, 52% in EUR, 41% in NA, and only 19% in AUS received adjuvant chemotherapy with/without external beam radiotherapy (EBRT). No patient (0%) in AUS had HRHFs that warranted EBRT.

Orbital tumor recurrence, systemic metastasis, and tumor-related death were seen in 60 (4%), 98 (7%), and 83 (6%) patients at a mean follow-up duration of 41 months (median, 35 months; range, <1–149 months). Tumor recurrence (10%), systemic metastasis (12%), and death (10%) were highest in SA ($P = 0.001$, $P = 0.0005582$, and $P = 0.009256$ respectively) and the lowest (all 0%) in AUS. The mean interval between enucleation and orbital tumor recurrence was the shortest in AS at 5 months (median, < 1 month; range, <1–36 months) and the longest in NA at 32 months (median, 9 months; range, 4–83 months) with the difference being statistically significant ($P < 0.001$) (Table 4).

Kaplan–Meier estimates of outcomes showed significant differences between continents for local recurrence and metastasis at 1 year, 2 years, 3 years, and 6 years and death estimates at 2 years, 3 years, and 6 years. The estimates of local recurrence, metastasis, and tumor-related death were the highest for SA (12%, 13%, and 11%, respectively) and the lowest for AUS (0%, 0%, and 0%, respectively) (Table 5) (Figure 1).

Discussion

The incidence and mortality of several cancers exhibit a great deal of variation in different parts of the world and different populations.[22] These geographic differences have been partly attributed to race, ethnicity, lifestyle, environment, genetic polymorphisms, epigenetic alterations, and immune/inflammatory responses. A large majority of the differences, however, are still unexplained.[22,23] Evidence on

Table 3. Histopathological Features of Primarily Enucleated Retinoblastoma Eyes in 1,426 Patients Across Five Continents

Feature	All Cases, n = 1,426, n (%)	Asia, n = 923, n (%)	Australia, n = 27, n (%)	Europe, n = 120, n (%)	North America, n = 162, n (%)	South America, n = 194, n (%)	*P*
Tumor growth pattern (n=1,342)							
Endophytic	642 (48)	424 (48)	1 (33)	67 (56)	43 (27)	107 (62)	0.001*
Exophytic	287 (21)	182 (21)	2 (66)	16 (13)	64 (40)	23 (13)	0.001†
Mixed pattern	370 (28)	249 (28)	0 (0)	32 (27)	48 (30)	41 (24)	0.009134‡
Diffuse infiltrating	37 (3)	25 (3)	0 (0)	4 (3)	6 (4)	2 (1)	0.4494
Tumor differentiation (n=1,366)							
Well differentiated	250 (18)	205 (23)	0 (0)	10 (8)	24 (15)	11 (6)	<0.001§
Moderately differentiated	498 (36)	335 (37)	0 (0)	34 (28)	52 (33)	77 (43)	0.000487¶
Poorly differentiated	471 (34)	292 (32)	1 (10)	19 (16)	81 (51)	78 (44)	0.001**
Undifferentiated	128 (10)	56 (6)	0 (0)	57 (48)	3 (2)	12 (7)	<0.001††
Tumor infiltration							
AC seeds	184 (13)	119 (13)	1 (4)	16 (13)	14 (9)	34 (18)	0.07927
Iris	114 (8)	91 (10)	0 (0)	9 (8)	8 (5)	6 (3)	0.004412‡‡
Trabecular meshwork	69 (5)	53 (6)	0 (0)	5 (4)	10 (6)	1 (<1)	0.02035§§
Schlemm canal	47 (3)	41 (4)	0 (0)	3 (3)	1 (<1)	2 (1)	0.01946
Ciliary body	101 (7)	70 (8)	0 (0)	9 (8)	9 (6)	13 (7)	0.548
Choroid	670 (47)	414 (45)	6 (22)	85 (71)	49 (30)	116 (60)	0.001¶¶
Minor	287 (20)	131 (14)	4 (15)	70 (58)	18 (11)	64 (33)	<0.001***
Massive	383 (27)	283 (31)	2 (7)	15 (13)	31 (19)	52 (27)	0.001†††
Optic nerve	959 (67)	601 (65)	4 (15)	103 (86)	115 (71)	136 (70)	0.001‡‡‡
Prelamina	319 (22)	159 (17)	3 (11)	57 (48)	56 (35)	44 (23)	0.001§§§
Lamina cribrosa	218 (15)	140 (15)	1 (4)	27 (23)	17 (10)	33 (17)	0.02716
Postlamina	335 (23)	245 (27)	0 (0)	19 (16)	34 (21)	37 (19)	0.0005819¶¶¶
Transected cut end	87 (6)	57 (6)	0 (0)	0 (0)	8 (5)	22 (11)	0.0007057****
Combination of prelaminar/laminar optic nerve and <3 mm of choroid	348 (24)	182 (20)	3 (11)	71 (59)	29 (18)	63 (32)	<0.001††††
Sclera	70 (5)	48 (5)	0 (0)	5 (4)	3 (2)	14 (7)	0.1277
Partial thickness	60 (4)	38 (4)	0 (0)	5 (4)	3 (2)	14 (7)	0.09944
Full thickness	10 (<1)	10 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0.2408
Extrascleral tissue	47 (3)	37 (4)	0 (0)	1 (<1)	1 (<1)	8 (4)	0.06798
8th edition AJCC staging							
pT1	655 (46)	420 (46)	24 (89)	37 (31)	91 (56)	83 (43)	0.001‡‡‡‡
pT2a	138 (10)	53 (6)	1 (4)	48 (40)	6 (4)	30 (15)	<0.001§§§§
pT2b	27 (2)	19 (2)	0 (0)	5 (4)	3 (2)	0 (0)	0.1016
pT3a	153 (11)	109 (12)	2 (7)	9 (8)	17 (11)	16 (8)	0.4062
pT3b	283 (20)	202 (22)	0 (0)	15 (13)	33 (20)	33 (17)	0.006749
pT3c	52 (4)	36 (4)	0 (0)	5 (4)	3 (2)	8 (4)	0.5757
pT3d	8 (<1)	8 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0.3565
pT4	110 (8)	76 (8)	0 (0)	1 (<1)	9 (6)	24 (12)	0.001505¶¶¶¶

*Post hoc analysis showed that AS was significantly different from AUS and NA; AUS was significantly different from EU and SA; EU was significantly different from NA; NA was significantly different from SA.

†Post hoc analysis showed that AS was significantly different from NA; AUS was significantly different from NA; EU was significantly different from NA; NA was significantly different from SA.

‡Post hoc analysis showed that AS was significantly different from AUE and SA.

§Post hoc analysis showed that AS was significantly different from EU and SA.

¶Post hoc analysis showed that AS was significantly different from AUE; AUE was significantly different from EU, NA, and SA.

**Post hoc analysis showed that AS was significantly different from ASU, EU, and NA; AUS was significantly different from NA and SA; EU was significantly different from NA and SA; NA was significantly different from SA.

††Post hoc analysis showed that AS was significantly different from EU; AUS was significantly different from EU; EU was significantly different from NA and SA.

‡‡Post hoc analysis showed that AS was significantly different from SA.

§§Post hoc analysis showed that AS was significantly different from SA.

¶¶Post hoc analysis showed that AS was significantly different from EU, NA, and SA; AUS was significantly different from EU and SA; EU was significantly different from NA; NA was significantly different from SA.

***Post hoc analysis showed that AS was significantly different from EU and SA; AUS was significantly different from EU; EU was significantly different from NA and SA; NA was significantly different from SA.

†††Post hoc analysis showed that AS was significantly different from EU and NA; EU was significantly different from SA.

‡‡‡Post hoc analysis showed that AS was significantly different from AUS and EU; AUS was significantly different from EU, NA, and SA; EU was significantly different from NA and SA.

§§§Post hoc analysis showed that AS was significantly different from EU and NA; AUS was significantly different from EU; NA was significantly different from SA.

¶¶¶Post hoc analysis showed that AS was significantly different from AUS.

****Post hoc analysis showed that EU was significantly different from SA.

††††Post hoc analysis showed that AS was significantly different from EU and SA; AUS was significantly different from EU; EU was significantly different from NA and SA; NA was significantly different from SA.

‡‡‡‡Post hoc analysis showed that AS was significantly different from AUS and EU; AUS was significantly different from EU and SA; EU was significantly different from NA.

§§§§Post hoc analysis showed that AS was significantly different from EU and SA; AUS was significantly different from EU; EU was significantly different from NA and SA; NA was significantly different from SA.

¶¶¶¶Post hoc analysis showed that EU was significantly different from SA.

Table 4. Treatment and Outcomes of 1,426 Retinoblastoma Patients From Five Continents Who Underwent Primary Enucleation

Feature	All Cases, n = 1,426, n (%)	Asia, n = 923, n (%)	Australia, n = 27, n (%)	Europe, n = 120, n (%)	North America, n = 162, n (%)	South America, n = 194, n (%)	*P*
Adjuvant treatment							
None	664 (47)	396 (43)	22 (81)	58 (48)	96 (59)	92 (47)	0.001*
IVC	704 (49)	508 (55)	5 (19)	50 (42)	64 (40)	77 (40)	0.001†
IVC + EBRT	57 (4)	18 (2)	0 (0)	12 (10)	2 (1)	25 (13)	0.001‡
No. of cycles of chemotherapy Mean (median, range)	6 (6, 1–12)	6 (6, 1–12)	6 (6, 6)	4 (4, 2–6)	6 (6, 4–11)	6 (6, 2–6)	<0.001§
EBRT dose (Gy) Mean (median, range)	44 (45, 30–50)	40 (40, 40–45)	Na	50 (50, 50)	NA	43 (45, 30–50)	<0.001¶
Outcomes							
Tumor recurrence in orbit	60 (4)	37 (4)	0 (0)	0 (0)	3 (2)	20 (10)	0.001**
Interval between enucleation and orbital tumor recurrence (months)	7 (4, <1–83)	5 (<1, <1–36)	Na	Na	32 (9, 4–83)	11 (9, 1–42)	<0.001††
Systemic metastasis	98 (7)	66 (7)	0 (0)	1 (<1)	7 (4)	24 (12)	0.0005582‡‡
Interval between enucleation and systemic metastasis (months)	10 (8, <1–83)	10 (9, <1–41)	Na	7 (6)	17 (6, <1–83)	9 (8, 2–25)	0.37
Death	83 (6)	57 (6)	0 (0)	2 (2)	5 (3)	19 (10)	0.009256
Interval between enucleation and death (months)	13 (11, <1–72)	14 (11, <1–72)	Na	10 (10, 7–12)	10 (10, 6–11)	12 (11, 3–26)	0.78
Follow-up duration (months) Mean (median, range)	41 (35, <1–149)	34 (28, <1–149)	73 (73, 8–135	59 (56, <1–139)	51 (46, <1–123)	53 (50, 1–138)	<0.001§§

IVC, intravenous chemotherapy; EBRT, external beam radiotherapy; Na, not applicable; NA, not available.

*Post hoc analysis showed that AS was significantly different from AUS and NA; AUS was significantly different from EU and SA.

†Post hoc analysis showed that AS was significantly different from AUS, NA, and SA.

‡Post hoc analysis showed that AS was significantly different from EUS and SA; EU was significantly different from NA; NA was significantly different from SA.

§Post hoc analysis showed that EU was significantly different from AS; EU was significantly different from NA; SA was significantly different from AUS.

¶Post hoc analysis showed that AS was significantly different from NA and EU; NA was significantly different from EU; SA was significantly different from AUS.

**Post hoc analysis showed that AS was significantly different from SA; EU was significantly different from SA; NA was significantly different from SA.

††Post hoc analysis showed that AS was significantly different from NA and SA; EU was significantly different from NA; NA was significantly different from SA.

‡‡Post hoc analysis showed that EU was significantly different from SA.

§§Post hoc analysis showed that AS was significantly different from EU, AUS, and SA; NA was significantly different from AUS; SA was significantly different from AUS.

intercontinental studies on the common cancers in the world, such as the lung and breast, have shown heterogeneity in presentation and survival based on region.[24,25] Although the most common pediatric intraocular malignancy,[25] RB is a rare cancer, and its global perspective is evolving. The literature from collaborative intercontinental studies on RB is increasing at a steady pace, and reports from the last decade have highlighted disparities in the clinical presentation and outcomes of RB, with a large majority of the differences attributed to the economic status of the country of origin.[6–8] Studies on histopathological features of RB are limited to reports from individual centers,[3,4,12–17] and a few studies have explored intercontinental differences.[16,17] Kaliki et al[16] compared the HRHFs between two RB treatment centers in India and the United States and noted greater HRHFs in India (30%) than United States (23%) but no difference in outcomes owing to robust adjuvant therapeutic regimes. Tomar et al reviewed data from RB treatment centers spread across six continents and noted that 30% of primarily enucleated eyes with RB had HRHFs. The latter study was aimed at identifying clinical features predictive of HRHFs, and no comparisons were made based on the country or region.[17]

In this study of 1,426 primarily enucleated eyes, HRHFs (based on the individual center's criteria) were seen in 50% of the patients, which is higher than the previously reported multinational studies.[16,17] Invasion of partial thickness sclera, full thickness sclera, and extrascleral orbit was seen in 60 (4%), 10 (<1%), and 47 (3%) eyes, respectively, all of which were clinically classified as an intraocular disease. Thus, the presence of HRHFs is quite high in eyes with

Table 5. Kaplan–Meier Analysis of Outcomes of 1,426 Retinoblastoma Patients From Five Continents Who Underwent Primary Enucleation

	All Cases, n = 1,426, n (%)		Asia, n = 923, n (%)		Australia, n = 27, n (%)		Europe, n = 120, n (%)		North America, n = 162, n (%)		South America, n = 194, n (%)		
Feature	n	% Estimate	n	% Estimate	n	% Estimate	n	% Estimate	n	% Estimate	n	% Estimate	*P*
Local tumor recurrence													
3 months	1,269	0.5%	816	1%	27	0%	89	0%	149	0%	191	1%	0.55
6 months	1,202	1%	758	1%	27	0%	87	0%	147	1%	186	3%	0.19
1 year	1,084	2%	696	2%	27	0%	86	0%	143	2%	169	6%	0.015
2 years	856	4%	493	4%	25	0%	80	0%	121	2%	145	11%	<0.001
3 years	650	4%	341	4%	21	0%	73	0%	99	2%	124	11%	<0.001
5 years	248	5%	105	5%	16	0%	26	0%	51	2%	55	12%	<0.001
Systemic metastasis													
3 months	1,269	1%	816	1%	27	0%	89	0%	149	2%	191	0%	0.25
6 months	1,202	1%	758	2%	27	0%	87	0%	147	2%	186	2%	0.39
1 year	1,084	4%	696	4%	27	0%	86	2%	143	4%	169	8%	0.03
2 years	856	6%	493	6%	25	0%	80	2%	121	5%	145	12%	0.001
3 years	650	6%	341	7%	21	0%	73	2%	99	5%	124	13%	0.006
5 years	248	7%	105	8%	16	0%	26	2%	51	5%	55	13%	0.001
Death													
3 months	1,269	0.5%	816	1%	27	0%	89	0%	149	0%	191	0%	0.41
6 months	1,202	1%	758	2%	27	0%	87	0%	147	0%	186	1%	0.09
1 year	1,084	3%	696	4%	27	0%	86	1%	143	3%	169	4%	0.23
2 years	856	6%	493	7%	25	0%	80	2%	121	3%	145	10%	0.003
3 years	650	7%	341	8%	21	0%	73	2%	99	3%	124	11%	0.001
5 years	248	8%	105	10%	16	0%	26	2%	51	3%	55	11%	0.001

n, number of patients with the defined follow-up duration.

RB undergoing primary enucleation, and thorough histopathological assessment is crucial for appropriate management and optimal outcomes.

There were striking differences in tumor histopathology between different continents in this study. First, endophytic tumors were more common in AS, EUR, and SA, whereas exophytic were more common in AUS and NA. Endophytic tumors have a propensity for vitreous seeding and exophytic tumors for choroidal and optic nerve invasion.[26–28] Palzzi et al noted that endophytic tumors had higher rates of positive family history, and exophytic tumors more often resulted in glaucoma.[27] In our study, the highest number of familial patients was seen in NA, but these tumors showed a higher % of exophytic (40%) than endophytic morphology (27%). However, eyes from AUS with predominantly exophytic tumors (66%) did show elevated intraocular pressures and greater corneal diameters when compared with other continents. A mixed growth pattern has been described to be associated with a higher IIRC group and neovascular glaucoma by Nawaiseh et al in a Turkish cohort,[28] and this trend was seen in our study as well. NA had the highest number of a mixed growth pattern (30%) among all the continents, along with the highest number of NVI (46%), secondary glaucoma (49%), and IIRC group E eyes (95%). However, this did not translate to worse outcomes about orbital tumor recurrence, metastasis, or death in NA.

The degree of tumor differentiation also varied greatly between continents. Retinoblastoma is known to exhibit lesser differentiation with time and advancing age.[29] This was not reflected in our study. Both EUR and NA had a mean age of presentation of 28 months and a mean duration of symptoms of 3 months. However, the highest proportion of poorly differentiated RB was seen in NA, and the highest proportion of undifferentiated RB was seen in EUR, contrary to the expected trend in the timeline of the disease.

On comparison of HRHFs between continents, there were significant differences. Patients in AS and SA had a higher percentage of HRHFs compared with AUS, EUR, and NA. An advanced pT stage was more common in SA. Outcomes largely corroborated with the pT stage of tumors, with a 6-year risk of orbital tumor recurrence, systemic metastasis, and disease-related death being highest in SA ($P < 0.001$). The lowest number of tumor-related events was seen in AUS, which had the highest number of pT1 stages.

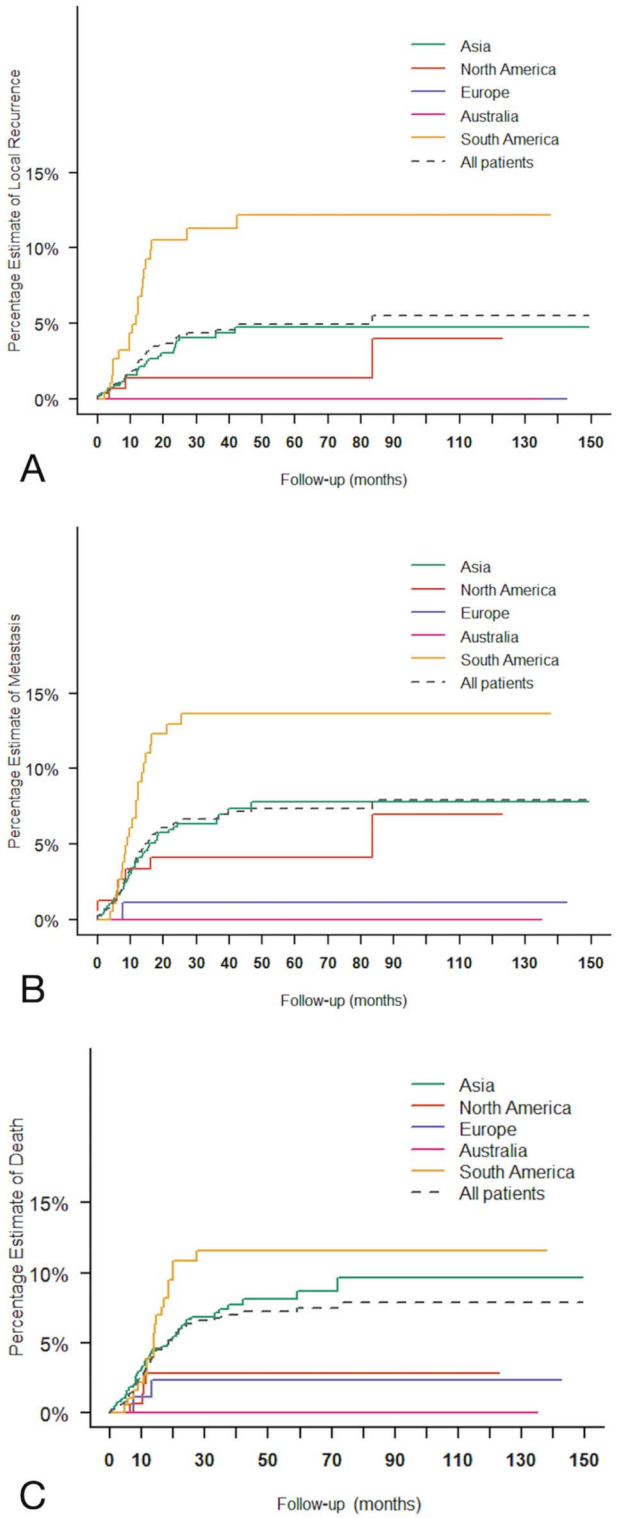

Fig. 1. Kaplan–Meier curves in different continents for retinoblastoma after primary enucleation: (**A**) tumor recurrence, (**B**) metastasis, and (**C**) tumor-related death.

This study has identified intercontinental variations in histopathological features of primarily enucleated RB eyes in a large cohort. The reason for these geographical differences is unexplored. In various cancers, race and ethnicity have been shown to play an important role in cancer susceptibility and survival, largely attributed to tumor gene polymorphisms and epigenetic and transcriptome variations.[23] Mutations in various oncogenes have been identified that vary between ethnicities.[23] RB is considered a prototypical genetic cancer, but there is evolving evidence that it is a complex trait with variations in phenotypic expression.[30] Afshar et al[31] demonstrated worse histopathological features in RB, such as higher histological grade and anaplasia, in the presence of mutations beyond *RB1*, including *MYC-N, MDM4, RAF1, BCOR*, *ARID1A, MGA, FAT1*, and *ATRX*. These factors have not been explored in our cohort. Delayed health-seeking behavior due to poor accessibility or awareness may also play a role in the intercontinental differences in HRHFs, with a higher probability of tumor invasion in patients undergoing delayed primary enucleation. It is possible that the differences in HRHFs reflect late presentations or delayed diagnoses in inadequately funded healthcare systems that vary between countries and continents, which could not be assessed in this study. Last, with data drawn from different nations and continents, variations in the reporting of histopathological data could exist. However, this is likely to be minimal for RB as tumor features have been objectively defined.[32]

The foremost strength of this study is the large sample size and the availability of histopathological data on RB from across the world. This is a first-of-its-kind study with a large sample size to explore the spectrum of histopathological risk factors of RB across several continents. It paves the way for further research on understanding the factors that influence the histomorphology of RB in different parts of the world. This study, however, has certain inherent limitations of a retrospective study. Although centers from all countries were approached for the study, the participation was subject to the discretion of the center's leading ocular oncologist. As a result, no patients could be enrolled from Africa due to lack of histopathology details in most patients, and the South American continent was represented by only one country, Peru. Although HRHF is a major contributor to the prognostication of survival in RB, being a pan-continental study, several factors may have a confounding role to play, which include the status of the contralateral eye, socio–economic parameters, awareness, education, access to medical care, and local insurance policies. Treatment protocols such as indication for primary enucleation and decision for adjuvant chemotherapy were based on the individual center's facilities and treatment protocols.

To conclude, this study provides the burden of HRHFs across the world and demonstrates the intercontinental heterogeneity in the histomorphology of

RB. Eyes from AS had the highest incidence of massive choroidal invasion and postlaminar optic nerve invasion, while those from SA had the highest involvement of the transected margin of the optic nerve. SA and AS had a higher risk of orbital tumor recurrence, systemic metastasis, and death compared with AUS, EUR, and NA.

Key words: eye, tumor, retinoblastoma, chemotherapy, enucleation, high-risk features, histopathology.

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