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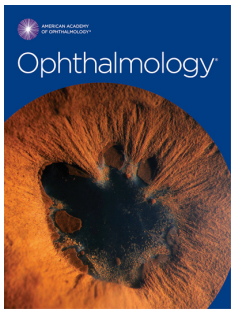

Retinoblastoma in Asia: Clinical presentation and Treatment Outcomes in 2112 patients from 33 countries

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Retinoblastoma in Asia: Clinical presentation and Treatment Outcomes in 2112 patients from 33 countries

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Précis:

Analysis of 2112 Asian patients from 33 countries with retinoblastoma revealed heterogeneity in clinical presentation and outcomes between the regions of Asian continent with better outcomes in East Asia and poorer outcomes in South-East Asia.

Keywords:

Eye

Tumor

Retinoblastoma

Asia

Abstract

Purpose: To describe the clinical presentation and treatment outcomes of children diagnosed with retinoblastoma (RB) in the year 2017, throughout Asia.

Design: Multi-national prospective study including treatment-naïve patients diagnosed with retinoblastoma in Asia during 2017 and followed up thereafter.

Participants: A total of 2112 patients (2797 eyes) from 96 RB treatment centers in 33 Asian countries.

Intervention: Chemotherapy, radiotherapy, enucleation, orbital exenteration

Main Outcome Measures: Enucleation and death

Results: Within the cohort, 1021 (48%) patients were from South Asia (SA), 503 (24%) from East Asia (EA), 310 (15%) from South-East Asia (SEA), 218 (10%) from West Asia (WA) and 60 (3%) from Central Asia (CA). Mean age at presentation was 27 months (median, 23 months; range, <1 to 261 months). There were 1195 (57%) males and 917 (43%) females. The most common presenting complaints were leukocoria (72%) and strabismus (13%). Based on 8th edition American Joint Committee for Cancer, tumors were staged as cT1 (n=441; 16%), cT2 (n=951; 34%), cT3 (n=1136; 41%), cT4 (n=267; 10%), N1 (n=48; 2%), and M1 (n=129; 6%) at presentation. RB was treated with intravenous chemotherapy in 1450 (52%) eyes and 857 (31%) underwent primary enucleation. Three-year Kaplan-Meier estimates for enucleation and death were 33% and 13% for CA, 18% and 4% for EA, 27% and 15% for SA, 32% and 22% for SEA, 20% and 11% for WA ($p<0.0001$ and $p<0.0001$), respectively.

Conclusion: At the conclusion of this study, there was a significant heterogeneity in treatment outcomes of RB between the regions of Asian continent. East Asia displayed better outcomes with

116 higher rates of globe and life salvage, while South-East Asia had poorer outcomes compared to
117 the rest of Asia.
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Introduction

Retinoblastoma (RB) is the most common intraocular tumor in childhood with a global incidence of 1 in 16,000 to 18,000 live births.[1] Asia is the world's largest continent by area and population with an estimated crude birth rate of 17 per 1000 people.[2] A majority of the burden of RB arises from India, China, Indonesia, Pakistan, Bangladesh, and Philippines.[3]

A combination of various factors including heterogeneity in awareness, screening programs, national income levels, availability of expertise and resources impact the outcomes of children with RB in Asia.[3,4] Little is known however, about the presentation and outcomes of RB in different regions within the Asian continent. This study aims to investigate the clinical presentation, availability of resources for treatment and outcomes of RB in the different Asian regions.

Methods

The present study is a sub-analysis of The Global Retinoblastoma Presentation and Outcome studies, in which 96 RB treatment centers from 33 Asian countries participated.[5,6] Information was obtained from all participating centers in Asia for patients who enrolled in the study, from January 1st, 2017 to December 31st, 2017 and were followed-up thereafter. Data collected comprised age at onset of symptoms, age at presentation to the RB center, lag time between onset of symptoms and presentation, distance from patients home to RB treatment center, sex, family history of RB, presenting symptom, clinical features at presentation, classification according to the International Classification for Retinoblastoma (ICRB) group,[7] International Retinoblastoma Staging System (IRSS) stage,[8] 8th edition American Joint Committee for Cancer (AJCC) stage,[9] resources available at the treatment center, management and outcomes in children with RB who were enrolled in the study. The study was conducted in adherence to the

STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement.[10] This study adhered to the tenets of Declaration of Helsinki. Approval was obtained from the Institutional Review Board of the London School of Hygiene & Tropical Medicine (London, UK) and informed consent was waived. Individual participating centers acquired approval from their respective local ethics committees.

Patients were divided into groups based on the region of presentation and treatment: Central Asia (CA) (Azerbaijan, Kazakhstan, Kyrgzstan, Uzbekistan); East Asia (EA) (China, Japan, Mongolia, Russia, South Korea-Republic of Korea, Taiwan); South Asia (SA) (Bangladesh, India, Iran, Nepal, Pakistan, Sri Lanka); South-East Asia (SEA) (Indonesia, Laos-People's Democratic Republic, Malaysia, Philippines, Singapore, Thailand, Timor-Leste, Vietnam); and West Asia (WA) (Iraq, Israel, Jordan, Kuwait, Lebanon, Saudi Arabia, Turkey, United Arab Emirates, Yemen).[11,12] The demographic features, clinical presentation, AJCC stage, treatment facilities available, management and outcomes were analysed for each group.

Statistical analysis:

The statistical analysis was performed using STATA v14.2 (StataCorp, College Station, TX, USA). Descriptive measures included mean, median, range and proportion. Comparisons among the five regions (CA, EA, SA, SEA, WA) were performed by analysis of variance (ANOVA) for continuous data and Chi-square test for categorical data. A p-value of <0.05 was considered statistically significant. Post-hoc analysis of continuous data was performed by Bonferroni test. In multiple pairwise comparisons of categorical data among five regions, a p-value of <0.0125 was considered statistically significant after adjustment for Bonferroni correction. Kaplan-Meier survival analysis was performed to estimate the probabilities of enucleation and death. Log-rank test was used to test the equality of survival by region.

Results

A total of 2112 patients (2797 eyes) from 96 RB treatment centers in 33 countries of Asia were included in the study. By region, maximum cases were from SA (n=1021; 48%) followed by EA (n=503; 24%), SEA (n=310; 15%), WA (n=218; 10%) and CA (n=60; 3%) (Figure 1).

Demographics, socioeconomic factors and clinical features (Tables 1 & 2)

Mean age at presentation was 27 months (median, 23 months; range, <1 to 261 months) for all patients, higher in SA (30 months) and SEA (30 months) regions, and lower in CA (24 months), EA (24 months), and WA (25 months) regions ($p<0.0001$). More males (57%) were recruited than females in Asia with sex ratio being highest in CA (1.6) followed by SA (1.4) and WA had an inverse sex ratio (0.9). However, the differences in sex ratio were not significant between the regions. Mean lag time between onset of first symptom and presentation to RB treatment center was 5 months (median, 1 month; range, <1 to 93 months). Lag time was greatest for CA at a mean of 15 months (median, 8 months; range, <1 to 77 months) which was significantly different from all other regions ($p<0.0001$). Mean distance from patient's home to RB treatment center was highest for WA at 742 km (median, 205 km; range, <1 to 11952 km) and CA at 725 km (median, 480 km; range, <1 to 4955 km) ($p<0.0001$).

Leukocoria (72%) was the most common presenting symptom in all regions of Asia. Presenting complaint of strabismus was higher in WA (27%), CA (20%), EA (15%) and less common in SA (9%) and SEA (7%) ($p<0.0001$). Presenting complaint of proptosis was more common in SA (9%), and SEA (8%), and less common in EA (3%), WA (2%), and CA (0%) ($p<0.0001$). At the RB center, advanced disease (T3 or T4) was more common in CA (60%), SEA (57%), and SA (55%) compared to EA (39%) and WA (40%) ($p<0.001$). Compared to other

regions, SEA had more number of cases with lymph node metastasis (5%; p=0.029) and distant metastasis (9%; p=0.005) at presentation.

Resources available at the RB treatment center and treatment performed (Table 3 & 4)

Overall, in Asia, facilities for genetic testing were available for 36%, imaging for 100%, and pathology for 99% of patients. The option of enucleation was available at all centers included in this study. Intravenous chemotherapy (IVC) was available for nearly all patients (99%); while laser therapy was available for 90%, cryotherapy for 83%, intra-arterial chemotherapy (IAC) for 51%, intra-vitreal chemotherapy (IViC) for 77%, plaque radiotherapy for 25% and external beam radiotherapy (EBRT) for 76% patients. However, these varied significantly between the regions. No patient in CA included in this study had access to magnetic resonance imaging (MRI), less than half (42%) had access to cryotherapy and only 2% had access to IAC and IViC.

Overall, IVC was the primary treatment in a majority (52%) of the cases followed by enucleation (31%) throughout Asia except in SEA where enucleation was slightly higher than IVC (46% vs 41%). However, for bilateral RB, IVC was the most common treatment modality in all regions of Asia (100% in CA, 87% in EA, 76% in SA, 84% in SEA, and 78% in WA). IAC as the primary treatment ranged from 0% in CA to 13% in EA. Focal treatment with laser or cryotherapy was the primary modality in 5% of patients. Secondary treatment modalities included laser or cryotherapy (24%), IVC (20%), IAC (9%), IViC (8%), plaque radiotherapy (1%), EBRT (4%), enucleation (20%), orbital exenteration (<1%), vitrectomy (1%), periocular chemotherapy, intrathecal chemotherapy (<1%) and palliative care (<1%).

Outcomes (Tables 5 & 6)

Overall, globe salvage was achieved in 41% of all patients, highest in EA (48%) and lowest in SEA (27%) (p<0.001). At a mean follow-up period of 26 months (median, 32 months; range,

<1 to 51 months), metastasis was seen in 8% of all patients and was highest in SEA (17%) ($p<0.001$). Death from RB resulted in 8% of all patients and was highest in SEA (15%) ($p<0.001$). One-, 2-, and 3-year Kaplan-Meier (KM) estimates of enucleation were 29%, 32%, and 33% for CA, 14%, 15%, and 18%, for EA, 19%, 22%, and 27% for SA, 16%, 24%, and 32% for SEA, 10%, 16%, and 20% for WA ($p<0.0001$), respectively. One-, 2-, and 3-year KM estimates of death were 6%, 11%, and 13% for CA, 3%,4%, and 4% for EA, 8%, 13%, and 15% for SA, 14%, 19%, and 22% for SEA, 6%, 9%, and 11% for WA ($p<0.0001$), respectively.

Discussion

Asia is the largest continent in the world[2] with more than a half (52%) of global new RB cases within the 1-year inclusion period of 2017 being from Asia.[5] However, only about a third (37%, 96 of 260) of the world's RB treatment centers included in this survey catered to this burden.[5] In Asia, the mean age at presentation with RB was 27 months, which was slightly higher than the global average of 23 months.[5] The gender predilection for RB in Asia was comparable to the global gender predilection for RB, but CA and SA had male preponderance suggestive of possible sociocultural factors and gender bias in seeking care for RB in these regions.[13] Most patients were staged as AJCC T2 and T3 and ICRB groups D and E as seen with low and middle-income countries.[14] Consensus on uniform screening protocols and improving awareness could greatly aid in early detection of tumors.[4]

Genetic testing for the RB1 gene has been available for nearly 3 decades[15] but its availability is still limited in Asia, and only 36% of all cases that had access to genetic testing for RB1 gene. In stark contrast, Schofield et al from Australia have shown the cost-effectiveness of pre-implantation genetic diagnosis for RB survivors to ensure that the germline RB1 mutation is not carried forward to the subsequent generation.[16] There is immense scope for improvement in

this field in Asia which is a hub for growing population and RB survivors from improved treatment modalities.

About 4% of RB patients in Asia travelled across borders for treatment of RB.[17] In this context, availability of resources for RB treatment within a country holds importance. IVC was available for nearly all patients enrolled which was a hopeful prospect. IVC and enucleation were the most common primary treatment modalities. Other treatment options, crucial for adjuvant or second-line management in RB such as IViC, IAC, EBRT and plaque radiotherapy were less commonly available which reduces the globe salvage potential especially in eyes with persistent or recurrent tumors. There were a few centers in EA, SA, and SEA still performing orbital exenteration as the primary treatment of RB. Due to the unfavorable facial deformity following orbital exenteration and poorer prognosis, there has been a tendency to avoid performing this procedure and replace it with chemoreduction followed by extended enucleation, which is preferable for patients with orbital extension of RB.[18] Vitrectomy is not a standard treatment for RB due to the risk of extraocular tumor extension, though there is an emerging evidence of its benefit when used as a part of multimodal treatment in carefully selected cases.[19] In this series, vitrectomy was performed in 2 patients in EA. Of these two, one patient was lost to follow-up after the surgery and the other patient ultimately underwent enucleation despite multimodal globe salvage treatments. Overall, 3-year KM estimates for enucleation and death were 24% and 11% respectively. While a survival rate of >85% is encouraging, globe salvage is limited by late diagnosis and lack of facilities for adjuvant and/or second-line treatment.

From a regional perspective, CA had the highest mean lag time (15 months), greater mean distance from home to RB treatment center (725 km) corresponding to the middle-income status of CA countries.[13] As shown by Kaliki et al,[20] this corroborated with more advanced presentation

(AJCC T3: 53%) and higher 3-year KM estimate of enucleation at 33%. Despite the prolonged lag time, the age at presentation with RB was lower compared to WA, SEA, and SA at 24 months with age at onset of symptoms being the lowest compared to other regions of Asia at 11 months, suggestive of earlier age of onset/earlier detection of RB in patients from CA. All patients (100%) had access to IVC, 88% to IViC and 95% to EBRT which explains the lower rate of death (3-year KM estimate of 13%) despite late presentation. Favorable prognosis for life could also be attributed to a higher proportion of unilateral RB (73%), possibly of sporadic inheritance.[21] The lack of availability of IAC in RB treatment centers in CA, which is one of the promising rescue treatment modality for globe salvage, also explains the lower globe salvage rate. There may be a role of tumor genetics in influencing the globe salvage rate, which needs to be explored. Scope for improving outcomes in CA lies in overcoming gender bias in seeking care, improving awareness on RB and resource management to make globe salvage treatment options available at the RB treatment centers.

East Asia had the lowest mean age at presentation (24 months), greatest availability of genetic testing (71%) and IAC (70%), and lowest 3-year KM estimate of enucleation (18%) and death (4%). SA had a greater mean age at presentation (30 months), highest mean age at onset of symptoms (29 months) and a slightly higher sex ratio (1.4) probably attributable to national income level and social disparities in seeking RB treatment.[13,14] The majority of patients belonged to AJCC T3 (43%) and T2 (29%) stages. Even though availability of IVC, IAC, EBRT and focal therapies was promising in SA, 3-year KM estimate of enucleation (27%) and death (15%) were relatively higher owing to advanced disease at presentation. SEA had the greatest mean age at onset of symptoms (29 months), greatest fraction of patients presenting with AJCC T4 (15%) disease and highest 3-year KM estimate of enucleation (32%) and death (22%). Poor outcomes in SEA could

be related to advanced disease at presentation, treatment delay, and lack of access to preferred treatment modality. WA had the greatest mean distance from home to RB treatment center (742 km) suggesting the need for improving the accessibility to care in this region. Despite this limitation, the 3-year KM estimate of enucleation (20%) and death (11%) was better compared to CA, SA, and SEA. This could be related to availability of all treatment options in a greater proportion of RB centers in this region.

While improvement in public awareness about RB is needed for improving outcomes, reforms in health care system also play an important role. Enabling easy access to health care services for all patients and allowing them to have free universal health insurance coverage enables all children to be admitted to tertiary health centers for appropriate diagnosis and treatment free-of-cost.[22]

The strength of the study is its relatively large cohort size including patients from different parts of Asia. However, this study included only the centers who contributed data to the Global Retinoblastoma Study Group[5] and thus may have missed several patients presenting to the centers not contributing to the study, which remains the major limitation of the study. There was heterogeneity in the availability of resources and treatment protocols between different countries and different centers within a country which could influence the treatment outcomes at each center. This study reflects the situation from 2017 to mid-2021, which is most likely to have changed today due to various improvement efforts undertaken in the countries participating in this study.

In conclusion, there is significant heterogeneity in availability of resources and outcomes between the regions of Asian continent. Approaches to improve early detection of RB and improve parental adherence to medical recommendation in all regions while improving availability of

resources for treatment through collaborative networks could play a pivotal role in improving the outcomes.

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Figure legend:

Figure 1: Retinoblastoma in the 5 regions of Asia

Patients enrolled in the study belonged to Central Asia (Azerbaijan, Kazakhstan, Kyrgzstan, Uzbekistan); East Asia (China, Japan, Mongolia, Russia, South Korea-Republic of Korea, Taiwan); South Asia (Bangladesh, India, Iran, Nepal, Pakistan, Sri Lanka); South-East Asia (Indonesia, Laos-People's Democratic Republic, Malaysia, Philippines, Singapore, Thailand, Timor-Leste, Vietnam); and West Asia (Iraq, Israel, Jordan, Kuwait, Lebanon, Saudi Arabia, Turkey, United Arab Emirates, Yemen).

Figure 2: Kaplan-Meier estimate of enucleation in the 5 regions of Asia

Figure 3: Kaplan-Meier estimate of death in the 5 regions of Asia

Table 1: Retinoblastoma in 96 centres from 33 Asian countries: Demographics

Feature	Central Asia n=60 n (%)	East Asia n=503 n (%)	South Asia n=1021 n (%)	South-East Asia n=310 n (%)	West Asia n=218 n (%)	All cases n=2112 n (%)	p-value*
Age at presentation (months) Mean (median; range)	24 (19, <1 to 77)	24 (20, <1 to 137)	30 (24, <1 to 192)	30 (25, <1 to 261)	25 (20, <1 to 224)	27 (23; <1 to 261)	<0.0001[a]
Age at onset of symptoms (months) Mean (median; range)	11 (5, 1 to 70)	18 (12, <1 to 126)	29 (24, <1 to 144)	22 (19, <1 to 120)	24 (18, <1 to 221)	24 (19; <1 to 221)	<0.0001[b]
Lag time between onset of first symptom and presentation (months) Mean (median; range)	15 (8, <1 to 77)	5 (2, <1 to 78)	3 (1, <1 to 93)	8 (3, <1 to 43)	6 (1, <1 to 49)	5 (1, <1 to 93)	<0.0001[c]
Gender							0.02
Male	37 (62)	271 (54)	605 (59)	178 (57)	104 (48)	1195 (57)	
Female	23 (38)	232 (46)	416 (41)	132 (43)	114 (52)	917 (43)	
Sex ratio	1.6	1.2	1.4	1.3	0.9	1.3	1.000
Distance from home to RB treatment center (km) Mean (median; range)	725 (480; <1 to 4955)	524 (360, <1 to 3987)	395 (211, <1 to 11418)	179 (81, <1 to 4760)	742 (205, <1 to 11952)	438 (223; <1 to 11952)	<0.0001[d]
Tumor laterality							<0.0001[e]
Unilateral	44 (73)	361 (72)	648 (63)	234 (75)	137 (63)	1424 (67)	
Bilateral	16 (27)	142 (28)	373 (37)	76 (25)	81 (37)	688 (33)	
Family history of RB	1 (2)	11 (2)	52 (5)	13 (4)	17 (8)	94 (4)	0.007
Presenting symptom*							
Leukocoria	43 (72)	356 (71)	745 (73)	224 (72)	148 (68)	1516 (72)	0.62
Strabismus	12 (20)	77 (15)	96 (9)	22 (7)	58 (27)	265 (13)	<0.0001[f]
Proptosis	0 (0)	14 (3)	94 (9)	26 (8)	5 (2)	139 (7)	<0.0001[g]
Others	6 (10)	74 (15)	118 (12)	39 (13)	19 (9)	243 (12)	0.19
Noted on fundus screening	0 (0)	4 (<1)	9 (<1)	4 (1)	7 (3)	37 (2)	0.04

RB=retinoblastoma; SA=South Asia; EA=East Asia; SEA=South-East Asia; WA= West Asia; CA=Central Asia

*88 patients had both leukocoria and strabismus

(*p<0.0042 was considered after applying Bonferroni correction for multiple comparisons)

[a]Post-hoc analysis showed that only EA was significantly different from SA and SEA.

[b]Post-hoc analysis showed that CA was significantly different from SA, SEA and WA; EA was significantly different from SA; and SA was significantly different from SEA.

[c]Post-hoc analysis showed that CA was significantly different from EA, SA, SEA and WA; EA was significantly different from SEA; and SA was significantly different from SEA.

[d]Post-hoc analysis showed that CA was significantly different from SA and SEA; EA was significantly different from SA, SEA and WA; SA was significantly different from SEA and WA; and SEA was significantly different from WA.

[e]Post-hoc analysis showed that EA was significantly different from SA; SA was significantly different from SEA; and SEA was significantly different from WA.
[f]Post-hoc analysis showed that CA was significantly different from SEA; EA was significantly different from SA, SEA and WA; and WA was significantly different from SA and SEA.
[g]Post-hoc analysis showed that EA was significantly different from SA and SEA; and WA was significantly different from SA and SEA.

Table 2: Retinoblastoma in 96 centres from 33 Asian countries: Tumor classification

Feature	Central Asia n=76 eyes of 60 patients n (%)	East Asia n=644 eyes of 503 patients n (%)	South Asia* n= 1391 eyes of 1021 patients n (%)	South-East Asia n=386 eyes of 310 patients n (%)	West Asia n=298 eyes of 218 patients n (%)	All cases n=2797 eyes in 2112 patients n (%)	p-value
AJCC 8th edition*							
T1	7 (9)	91 (14)	230 (17)	46 (12)	67 (22)	441 (16)	0.001[a]
T2	24 (32)	299 (46)	397 (29)	120 (31)	111 (37)	951 (34)	<0.001[b]
T3	40 (53)	236 (37)	594 (43)	162 (42)	104 (35)	1136 (41)	0.004
T4	5 (7)	18 (3)	170 (12)	58 (15)	16 (5)	267 (10)	<0.001[c]
N1	0 (0)	10 (2)	19 (2)	14 (5)	5 (2)	48 (2)	0.029
M1	1 (2)	18 (4)	69 (7)	29 (9)	12 (6)	129 (6)	0.005
ICRB*							
Group A	5 (7)	17 (3)	35 (3)	10 (3)	25 (9)	92 (4)	<0.001[d]
Group B	2 (3)	59 (9)	185 (15)	28 (8)	38 (13)	312 (12)	<0.001[e]
Group C	18 (25)	45 (7)	154 (13)	27 (8)	39 (14)	283 (11)	<0.001[f]
Group D	13 (18)	223 (36)	208 (17)	87 (26)	77 (27)	608 (24)	<0.001[g]
Group E	33 (46)	282 (45)	639 (52)	179 (54)	103 (37)	1236 (49)	0.008
IRSS*							
Stage 0	45 (59)	404 (63)	761 (55)	157 (41)	176 (59)	1543 (55)	<0.001[h]
Stage 1	24 (32)	198 (31)	371 (27)	151 (39)	87 (29)	831 (30)	<0.001[i]
Stage 2	2 (3)	9 (1)	62 (4)	11 (3)	15 (5)	99 (4)	0.005
Stage 3	3 (4)	14 (2)	132 (9)	36 (9)	6 (2)	191 (7)	<0.001[j]
Stage 4	2 (3)	19 (3)	65 (5)	31 (8)	14 (5)	131 (5)	0.005

*Two eyes couldn't be classified since they were retinomas. AJCC=American Joint Committee on Cancer classification; T=primary tumor; N=lymph node; M=distant metastasis; ICRB=International Classification of Retinoblastoma; IRSS=International Retinoblastoma Staging System; SA=Southern Asia; EA=Eastern Asia; SEA=South-East Asia; WA= Western Asia; CA=Central Asia

(*p<0.0031 was considered after applying Bonferroni correction for multiple comparisons)

[a]Post-hoc analysis showed that EA was significantly different from SA, SEA and WA; and SA was significantly different from WA.

[b]Post-hoc analysis showed that EA was significantly different from WA; and SEA was significantly different from WA.

[c]Post-hoc analysis showed that EA was significantly different from SA and SEA; and WA was significantly different from SA and SEA.
[d]Post-hoc analysis showed that EA, SA and SEA were significantly different from WA.
[e]Post-hoc analysis showed that CA, SA and SEA were significantly different from SA.
[f]Post-hoc analysis showed that CA was significantly different from EA, SA and SEA; EA was significantly different from SA and WA; and SEA was significantly different from WA.
[g]Post-hoc analysis showed that CA was significantly different from EA; EA was significantly different from SA, SEA and WA; and SA was significantly different from SEA and WA.
[h]Post-hoc analysis showed that EA was significantly different from SA and SEA; and CA, SA and WA were significantly different from SEA.
[i]Post-hoc analysis showed that EA, SA and WA were significantly different from SEA.
[j]Post-hoc analysis showed that EA was significantly different from SA and SEA; and, SA and SEA were significantly different from WA.

Table 3: Retinoblastoma in 96 centres from 33 Asian countries: Resources available at the centers for 2112 patients

Feature	Central Asia n=60 n (%)	East Asia n=503 n (%)	South Asia n=1021 n (%)	South-East Asia n=310 n (%)	West Asia n=218 n (%)	All cases n=2112 n (%)	p-value
Genetic testing	27 (45)	358 (71)	226 (22)	115 (37)	32 (15)	758 (36)	<0.001[a]
Imaging							
CT only	29 (48)	13 (3)	158 (15)	126 (41)	5 (2)	331 (16)	<0.001[b]
MRI only	0 (0)	23 (5)	425 (42)	66 (21)	116 (53)	630 (30)	<0.001[c]
Both CT and MRI	31 (52)	466 (93)	438 (43)	118 (38)	97 (44)	1150 (54)	<0.001[d]
Pathology	60 (100)	501 (100)	1021 (100)	310 (100)	210 (96)	2102 (99.5)	<0.001[e]
Laser therapy	52 (87)	489 (97)	978 (96)	234 (75)	151 (69)	1904 (90)	<0.001[f]
Cryotherapy	25 (42)	469 (93)	882 (86)	225 (73)	151 (69)	1752 (83)	<0.001[g]
Intravenous chemotherapy	60 (100)	495 (98)	1021 (100)	309 (99.7)	218 (100)	2103 (99.6)	<0.001[h]
Intra-arterial chemotherapy	1 (2)	351 (70)	565 (55)	73 (24)	96 (44)	1086 (51)	<0.001[i]
Intra-vitreal chemotherapy	53 (88)	473 (94)	872 (85)	73 (24)	151 (69)	1622 (77)	<0.001[j]
Plaque radiotherapy	1 (2)	32 (6)	393 (38)	28 (9)	82 (38)	536 (25)	<0.001[k]
External beam radiotherapy	57 (95)	336 (67)	851 (83)	193 (62)	165 (76)	1602 (76)	<0.001[l]

SA=Southern Asia; EA=Eastern Asia; SEA=South-East Asia; WA= Western Asia; CA=Central Asia; CT=computed tomography; MRI=magnetic resonance imaging
(*p<0.0042 was considered after applying Bonferroni correction for multiple comparisons)

[a]Post-hoc analysis showed that CA was significantly different from EA, SA and WA; EA was significantly different from SA, SEA and WA; SA was significantly different from SEA; and SEA was significantly different from WA.

[b]Post-hoc analysis showed that CA was significantly different from EA, SA and WA; EA was significantly different from SA and SEA; SA was significantly different from SEA and WA; and SEA was significantly different from WA.

[c]Post-hoc analysis showed that CA was significantly different from SA, SEA and WA; EA was significantly different from SA, SEA and WA; SA was significantly different from SEA and WA; and SEA was significantly different from WA.

[d]Post-hoc analysis showed that CA was significantly different from SA; and EA was significantly different from SA, SEA and WA.

[e]Post-hoc analysis showed that EA and SEA were significantly different from WA.

[f]Post-hoc analysis showed that CA was significantly different from EA and WA; EA was significantly different from SEA and WA; and SA was significantly different from SEA and WA.

[g]Post-hoc analysis showed that CA was significantly different from EA, SA, SEA and WA; EA was significantly different from SA, SEA and WA; and SA was significantly different from SEA and WA.
[h]Post-hoc analysis showed that none of the pairwise comparisons was significantly different.
[i]Post-hoc analysis showed that CA was significantly different from EA, SA, SEA and WA; EA was significantly different from SA, SEA and WA; SA was significantly different from SEA and WA; and SEA was significantly different from WA.
[j]Post-hoc analysis showed that CA was significantly different from SEA and WA; EA was significantly different from SA, SEA and WA; SA was significantly different from SEA and WA; and SEA was significantly different from WA.
[k]Post-hoc analysis showed that CA was significantly different from SA and WA; EA was significantly different from SA and WA; SA was significantly different from SEA; and SEA was significantly different from WA.
[l]Post-hoc analysis showed that CA was significantly different from EA, SEA and WA; EA was significantly different from SA; SA was significantly different from SEA and WA; and SEA was significantly different from WA.

Table 4: Retinoblastoma in 96 centres from 33 Asian countries: Treatment and outcomes

Feature	Central Asia n=76 eyes of 60 patients n (%)	East Asia n=644 eyes of 503 patients n (%)	South Asia* n= 1391 eyes of 1021 patients n (%)	South-East Asia n=386 eyes of 310 patients n (%)	West Asia n=298 eyes of 218 patients n (%)	All cases n=2797 eyes in 2112 patients n (%)	p-value
Primary treatment							
Observation*	0 (0)	0 (0)	2 (0)	0 (0)	0 (0)	2 (<1)	0.73
Laser or cryotherapy	0 (0)	22 (3)	78 (6)	7 (2)	22 (7)	129 (5)	<0.001[a]
IVC	54 (71)	319 (50)	787 (57)	159 (41)	131 (44)	1450 (52)	<0.001[b]
IAC	0 (0)	83 (13)	33 (2)	4 (1)	32 (11)	152 (5)	<0.001[c]
IViC	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<)	<0.001[d]
Plaque radiotherapy	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	1 (<1)	0.08
EBRT	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	N/A
Enucleation	20 (26)	205 (32)	351 (25)	179 (46)	102 (34)	857 (31)	<0.001[e]
Orbital exenteration	0 (0)	1 (<1)	6 (<1)	13 (3)	0 (0)	20 (<1)	<0.001[f]
Vitrectomy	0 (0)	2 (<1)	0 (0)	0 (0)	0 (0)	2 (<1)	0.15
Palliative treatment	0 (0)	0 (0)	17 (1)	4 (1)	0 (0)	21 (<1)	0.016
Treatment refusal	1 (1)	12 (2)	119 (9)	21 (5)	10 (3)	163 (6)	<0.001[g]
Additional treatment							
Laser or cryotherapy	16 (21)	221 (34)	150 (11)	52 (13)	78 (26)	669 (24)	<0.001[h]
IVC	32 (42)	117 (18)	76 (5)	80 (21)	68 (23)	562 (20)	<0.001[i]
IAC	1 (1)	141 (22)	31 (2)	12 (3)	41 (14)	259 (9)	<0.001[j]
IViC	2 (3)	83 (13)	44 (3)	6 (2)	30 (10)	213 (8)	<0.001[k]
Plaque radiotherapy	5 (7)	11 (2)	9 (1)	2 (1)	5 (2)	35 (1)	<0.001[l]
EBRT	2 (3)	12 (2)	44 (3)	16 (4)	7 (2)	105 (4)	0.26
Enucleation	27 (36)	102 (16)	171 (12)	72 (19)	42 (14)	568 (20)	<0.001[m]
Orbital exenteration	1 (1)	7 (1)	11 (1)	3 (1)	0 (0)	23 (<1)	0.50
Vitrectomy	0 (0)	22 (3)	7 (1)	0 (0)	1 (<1)	37 (1)	<0.001[n]
POC	0 (0)	8 (1)	0 (0)	0 (0)	3 (1)	11 (<1)	<0.001[o]
Intrathecal chemotherapy	0 (0)	0 (0)	1 (<1)	2 (1)	0 (0)	3 (<1)	0.12

Palliative care	0 (0)	0 (0)	7 (1)	0 (0)	0 (0)	18 (<1)	0.13
Abandonment of treatment	0 (0)	23 (4)	25 (2)	17 (4)	11 (4)	103 (4)	0.009
Outcomes							
Globe salvage	28 (37)	309 (48)	561 (40)	103 (27)	144 (48)	1145 (41)	<0.001[p]
Metastasis	3 (5)	33 (7)	114 (11)	54 (17)	21 (10)	227 (8)	<0.001[q]
Death	2 (3)	16 (3)	137 (13)	48 (15)	20 (9)	228 (8)	<0.001[r]

*2 eyes had stable retinoma. IVC=intravenous chemotherapy; IAC=intra-arterial chemotherapy; IViC=intra-vitreal chemotherapy; EBRT=external beam radiotherapy; POC=periocular chemotherapy; SA=Southern Asia; EA=Eastern Asia; SEA=South-East Asia; WA= Western Asia; CA=Central Asia

(*p<0.0018 was considered after applying Bonferroni correction for multiple comparisons)

[a]Post-hoc analysis showed that EA was significantly different from WA; SA was significantly different from SEA; and SEA was significantly different from WA.

[b]Post-hoc analysis showed that CA was significantly different from EA, SEA and WA; EA was significantly different from SA, SEA and WA; and SA was significantly different from SEA and WA.

[c]Post-hoc analysis showed that CA was significantly different from EA and WA; EA was significantly different from SA and SEA; and SA and SEA were significantly different from WA.

[d]Post-hoc analysis showed that none of the pair-wise comparisons was significantly different.

[e]Post-hoc analysis showed that CA was significantly different from SEA; EA was significantly different from SA and SEA; SA was significantly different from SEA and WA; and SEA was significantly different from WA.

[f]Post-hoc analysis showed that EA and WA were significantly different from SEA.

[g]Post-hoc analysis showed that EA was significantly different from SA and SEA; and SA was significantly different from WA.

[h]Post-hoc analysis showed that CA was significantly different from SA; EA was significantly different from SA and SEA; SA was significantly different from WA; and SEA was significantly different from WA.

[i]Post-hoc analysis showed that CA was significantly different from EA, SA, SEA and WA; EA was significantly different from SA; and SA was significantly different from SEA and WA.

[j]Post-hoc analysis showed that CA was significantly different from EA and WA; EA was significantly different from SA, SEA and WA; SA was significantly different from WA; and SEA was significantly different from WA.

[k]Post-hoc analysis showed that EA was significantly different from SA and SEA; SA was significantly different from WA; and SEA was significantly different from WA.

[l]Post-hoc analysis showed that only CA was significantly different from SEA.

[m]Post-hoc analysis showed that CA was significantly different from EA, SA, SEA and WA; and SA was significantly different from WA.

[n]Post-hoc analysis showed that only EA was significantly different from SA, SEA and WA.

[o]Post-hoc analysis showed that none of the pair-wise comparisons was significantly different.

[p]Post-hoc analysis showed that EA was significantly different from SA and SEA; and SEA was significantly different from SA and WA.

[q]Post-hoc analysis showed that EA was significantly different from SEA; and SEA was significantly different from SA and WA.

[r]Post-hoc analysis showed that only EA was significantly different from SA, SEA and WA.

Table 5: Retinoblastoma in 96 centres from 33 Asian countries: Kaplan-Meier survival estimates of enucleation

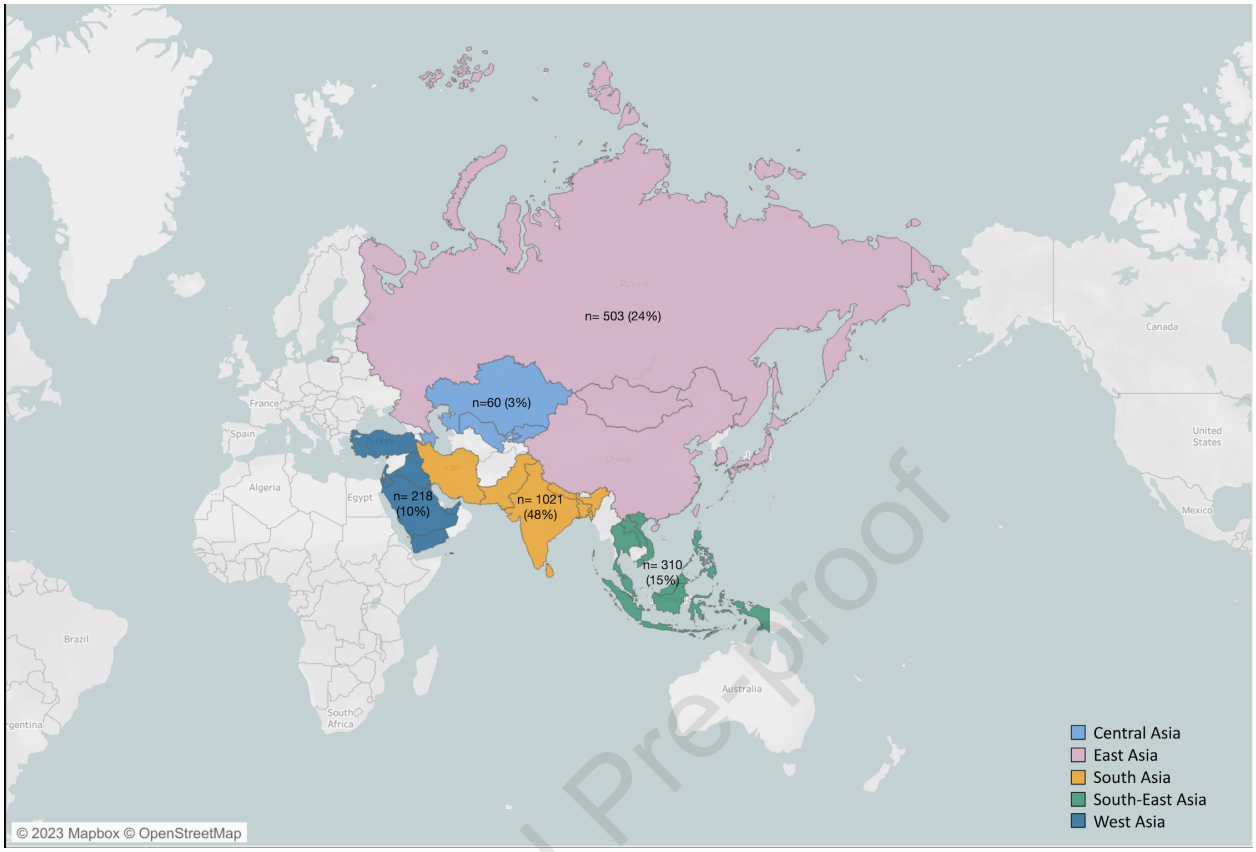
	Central Asia		East Asia		South Asia		South-East Asia		West Asia		All cases		p-value
Time	N	Est ± SE	N	Est ± SE	N	Est ± SE	N	Est ± SE	N	Est ± SE	N	Est ± SE	
3M	88	19.4% ± 3.8%	684	8.3% ± 1.0%	1338	8.8% ± 0.7%	308	5.3% ± 1.2%	308	3.7% ± 1.0%	2723	8.1% ± 0.5%	<0.0001
6M	81	24.1% ± 4.1%	645	11.6% ± 1.2%	1196	13.9% ± 0.9%	251	11.5% ± 1.8%	274	6.3% ± 1.4%	2444	12.6% ± 0.6%	
1Y	71	29.1% ± 4.4%	615	13.6% ± 1.3%	995	19.4% ± 1.1%	189	16.0% ± 2.2%	242	9.5% ± 1.7%	2109	16.8% ± 0.7%	
2Y	66	32.2% ± 4.6%	564	15.3% ± 1.3%	812	22.3% ± 1.1%	141	23.9% ± 2.7%	192	15.7% ± 2.2%	1769	20.1% ± 0.8%	
3Y	57	33.2% ± 4.6%	407	17.6% ± 1.4%	515	26.8% ± 1.3%	63	31.9% ± 3.3%	110	20.3% ± 2.6%	1145	24.0% ± 0.9%	
3.5Y	34	33.2% ± 4.6%	149	20.2% ± 1.6%	215	32.2% ± 1.6%	19	38.5% ± 4.1%	44	25.7% ± 3.5%	457	28.3% ± 1.0%	

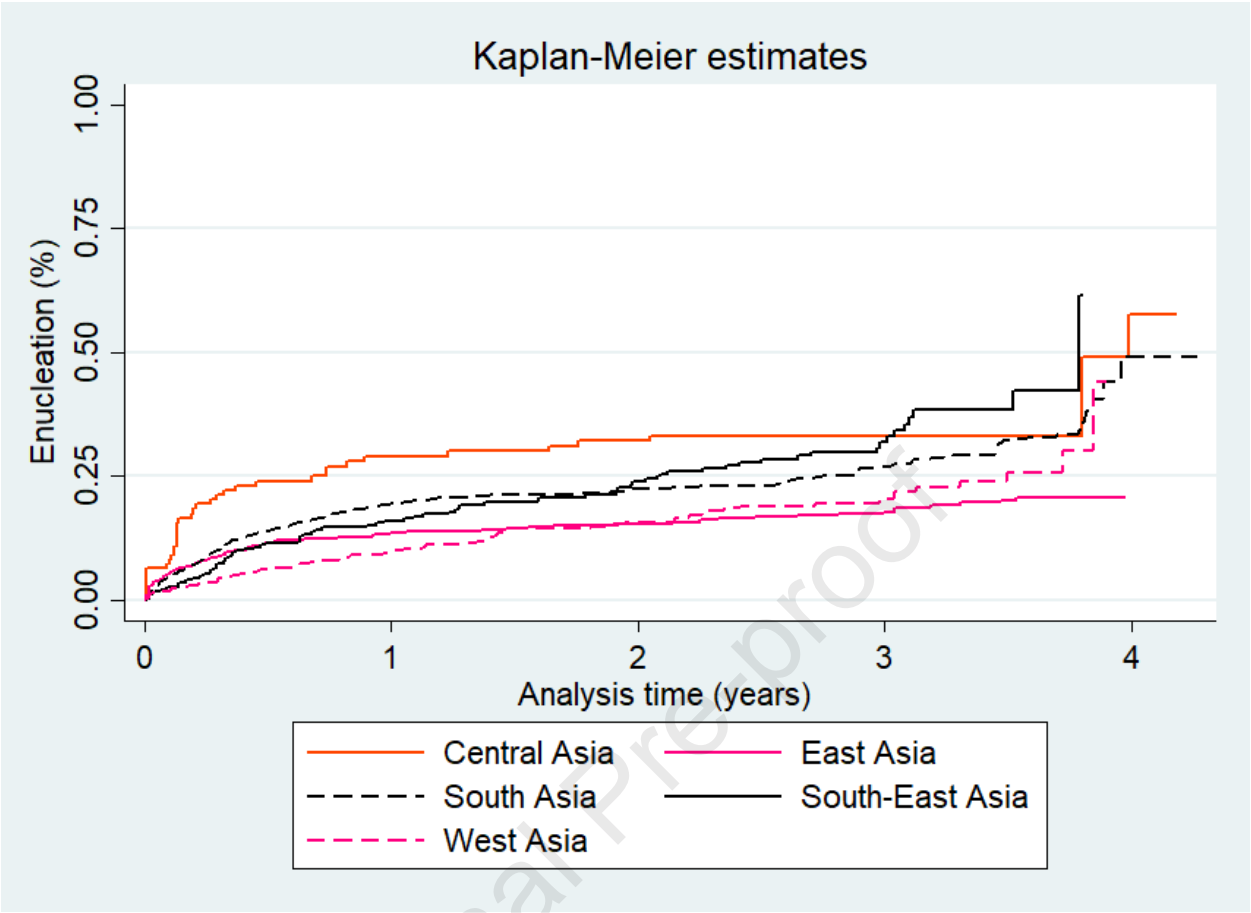
M = month; Y = year; N = number at risk; Est ± SE = Estimate ± standard error; 95% CI = 95% confidence interval

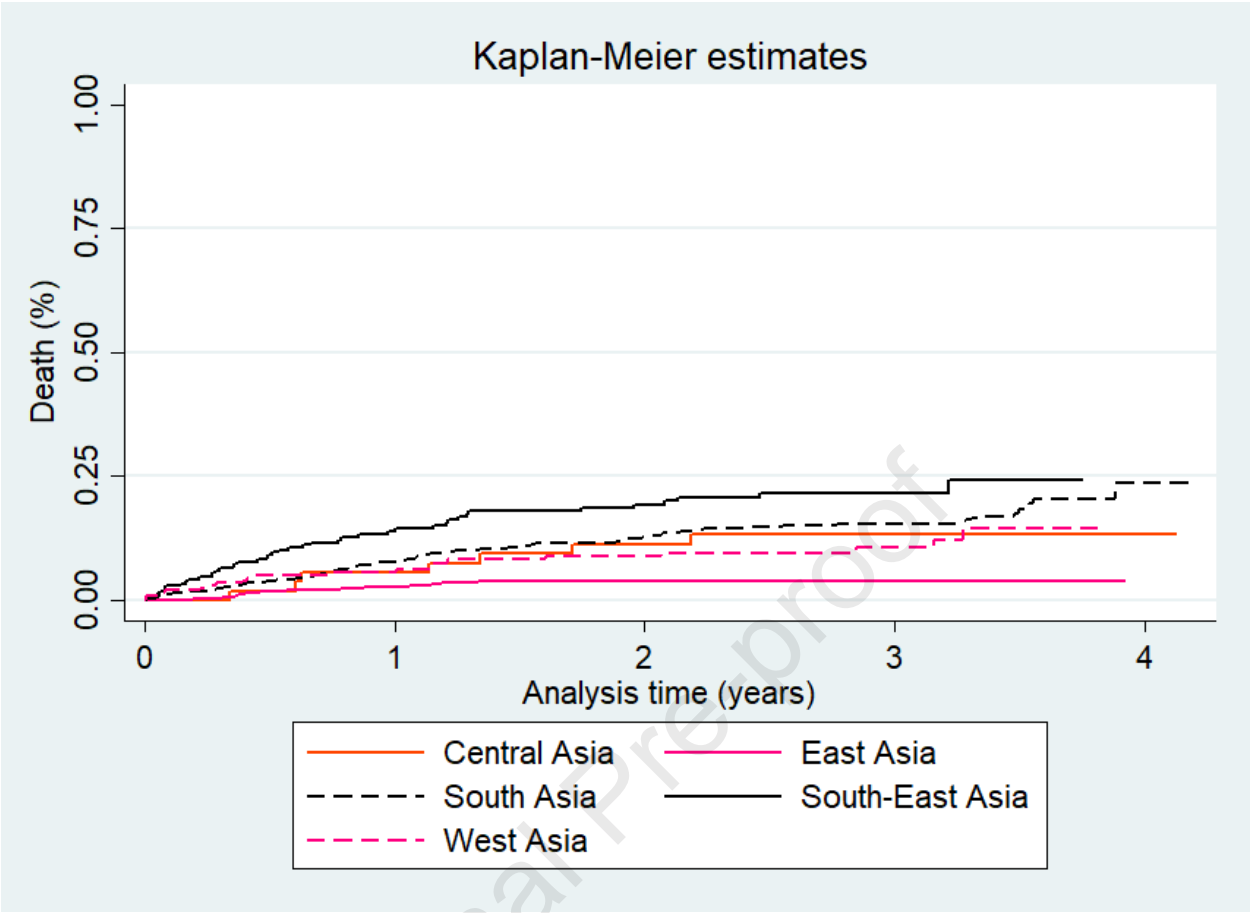
Table 6: Retinoblastoma in 96 centres from 33 Asian countries: Kaplan-Meier survival estimates of death

	Central Asia		East Asia		South Asia		South-East Asia		West Asia		All cases		p-value
Time	N	Est ± SE	N	Est ± SE	N	Est ± SE	N	Est ± SE	N	Est ± SE	N	Est ± SE	
3M	56	0%	442	0.2% ± 0.2%	853	1.8% ± 0.4%	221	4.6% ± 1.4%	196	2.4% ± 1.0%	1764	1.8% ± 0.3%	<0.0001
6M	54	1.9% ± 1.8%	430	1.8% ± 0.6%	815	3.9% ± 0.7%	193	9.1% ± 1.9%	172	5.0% ± 1.6%	1659	4.1% ± 0.5%	
1Y	51	5.6% ± 3.1%	417	2.7% ± 0.8%	720	7.7% ± 0.9%	152	13.9% ± 2.4%	157	5.6% ± 1.7%	1493	7.0% ± 0.6%	
2Y	47	11.2% ± 4.3%	386	3.9% ± 0.9%	595	12.6% ± 1.2%	114	19.3% ± 2.8%	131	8.8% ± 2.1%	1269	10.7% ± 0.8%	
3Y	42	13.2% ± 4.6%	257	3.9% ± 0.9%	355	15.3% ± 1.3%	47	21.6% ± 3.0%	75	10.6% ± 2.4%	770	12.4% ± 0.8%	
3.5Y	22	13.2% ± 4.6%	81	3.9% ± 0.9%	128	18.2% ± 1.7%	12	24.2% ± 4.0%	28	14.4% ± 3.5%	267	14.4% ± 1.0%	

M = month; Y = year; N = number at risk; Est ± SE = Estimate ± standard error; 95% CI = 95% confidence interval







Précis:

Analysis of 2112 Asian patients from 33 countries with retinoblastoma revealed heterogeneity in clinical presentation and outcomes between the regions of Asian continent with better outcomes in East Asia and poorer outcomes in South-East Asia.